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Review Article

A Review on Uses of Various Nanoparticles in the Treatment of Rheumatoid Arthritis

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A B S T R A C T

Rheumatoid arthritis (RA) is a most common autoimmune (auto-self: immune-immunity system). It is inflammatory in nature. If generally causes bone and cartilage destruction. Itaffect on joint clinical manifestationsof arthritis various from patient to patient. Now, new field comes into existence called use of nanoparticles and nanotechnology. It improves the pharmacokinetic as well as pharmacodynamics of rheumatoid arthritis drugs. Nanoparticles act on site of inflammation and delivery of therapeutic agent to that site. It also increases specificity of drugs and decrease side effects. These review summarize the current therapeutic strategies for rheumatoid arthritis. Nanotechnology or nanoparticles used in treatment of rheumatoid arthritis. Mostly focus on application of nanoparticles in treatment of rheumatoid arthritis.

Keyword: Autoimmune Disease, Rheumatoid Arthritis, Nanoparticles, Nanotechnology, Inflammation, Drug Delivery System,

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INTRODUCTION

Rheumatoid arthritis is most common autoimmune disease/disorder characterized by bone and cartilage destruction it primarily affects on joints [1]. It causes inflammation of synovium and increased thickness ofsynovium joint [2]. The ratio of RA male to female is 1:3 and mostly at age of 40-60 years. Variety of treatment available (NASIDs, GCS) but they have side effects. so, filed of nanotechnology/nanoparticles comes into existence.Rheumatoid arthritis is the most common inflammatory arthritis up to 0.75% of the Indian population. Various factors such as disease activity, socioeconomic, educational status, body mass index, spirituality, age and gender affects rheumatoid disease patient`s quality of life. Rheumatoid arthritis varies significantly from osteoarthritis, which is a degenerative joint disease affects only joint function in fig.1. Nanotechnology is a branch of pharmaceutical science that uses nanoparticles for treating disease such as rheumatoid arthritis. Tumor necrosis factor (TNF-α) plays an important role in pathogenesis of rheumatoid arthritis[3] Nanoparticles are easily penetrable and reduce inflammation because it accumulate on tissue. Different types of nanoparticles for treatment are liposomes, polymer magnetic nanoparticles, metal nanoparticles. These review summarize application of nanoparticles to treat rheumatoid, treat joint injuries and their process.

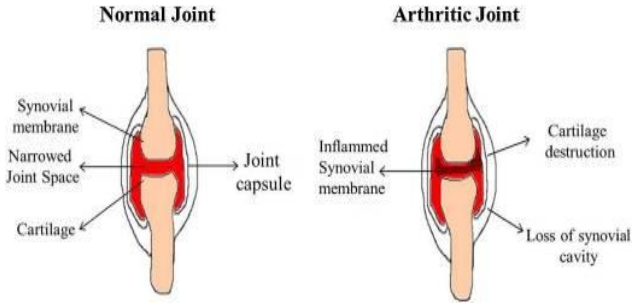

Figure 1: Comparison between (A) normal (B) rheumatoid arthritis joints.

CURRENT THERAPEUTIC STRATEGIES FOR RA:

Many therapeutic treatments are available for chronic inflammatory disorder/disease called rheumatoid arthritis.

Such as non-steroidal anti-inflammatory drugs (NSAIDs), disease-modifying anti- rheumatic drug (DMARD), glucocorticoids , bridging therapy (frequently used) , systemic GCs used as a co- therapy and it shows disease modifying effects in patient within two years of treatment. In fig.2.

But all these treatment has side effects for example NSAIDs has limited effectiveness.it is enabled to modify disease course.GCs it is affordable but it has many side effects , include cardiovascular disease , osteoporosis , infections (mostly prone to fungal infections) , it also impaired glucose metabolism.[4]

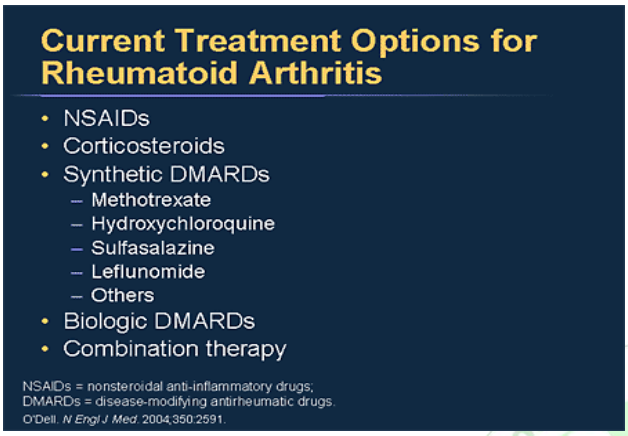

Figure 2: Current treatment options for RA

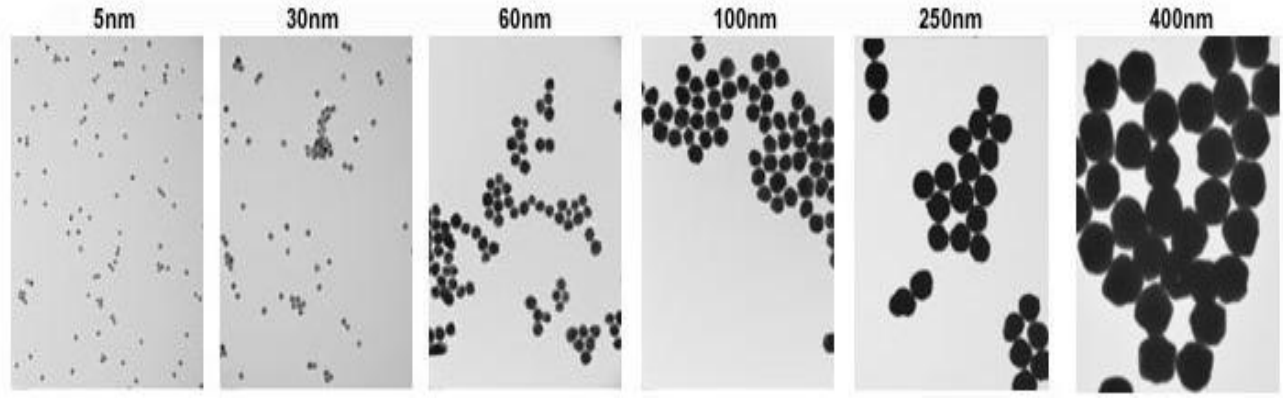

Figure 3: Different size of nanoparticles

TRADITIONAL NANOPARTICLES

The application of nanoparticles in treatment of RA is very simple it act as carrier of anti-inflammatory drugs by surface modification with the carrier, the drugs released at synovial joint site and accumulate on joint site and improve effect of drug. Organic polymer nanoparticles, liposomes, inorganic nanoparticles can be used as a carrier of anti-inflammatory drugs.[6,7]

Polymer nanoparticles

Polymer nanoparticles have good biocompatibility and biodegradability, also target specific organs and tissue. And mostly used as a drug carrier .anti- rheumatoid arthritis drugs absorbed in polymer nanoparticle and deliver to specific sites.

Most commonly used technique is modification of surface of nanoparticles with polyethylene glycol (PEG). Mostly used because it increases stability of drugs and reduce immunogenicity i.e not recognize easily[8]PCL-PEG micelles targeting to deliver low doses of dexamethasone for treatment of RA .Used mostly because micelles existed long time in systemic circulation and simultaneously accumulate or deposited in joint.(RA joint) . Dexamethasone delivery takes place at site and reduces inflammation or swelling, bone erosion. But it has some side effects [9].

Nanoparticles re-polarize macrophages from M1toM2[10]. In fig.4. Nanoparticles incorporated with hydrogel eucalyptus oil act as penetrant and it avoid first pass effect, it improves patient compliance and also reduces liver toxicity.

Dextran sulphate can be used as a carrier (MTX-DSNPs) in treatment of RA in fig. 4.

When MTX-DSNPs administered (in mice) it observed that they forms loose aggregates in inflamed joints, it is more effective it increases therapeutic effect.

NANOPARTICLES AND ITS APPLICATION

Nanoparticles and nanotechnology haswide application in pharmaceutical science. Nanoparticle is a particles formulation which is measured in scale called “nanometer”. Generally size ranges from 1to 100nm. In Fig.3. They have transparent appearance and lower precipitating time than other particles with size more than 100nm [5].

Different types of nanoparticles used for treatment of RA. They are as follows

Traditional Nanoparticles

Polymer nanoparticles

Liposomes

Metallic nanoparticles

Inorganic nanoparticles

Bionic Nanoparticles

Nanoparticle coated with cell membrane

Exosomes encapsulated nanoparticles

Material Itself with Anti-Inflammatory Property

Au clusters

Cationic nanoparticles

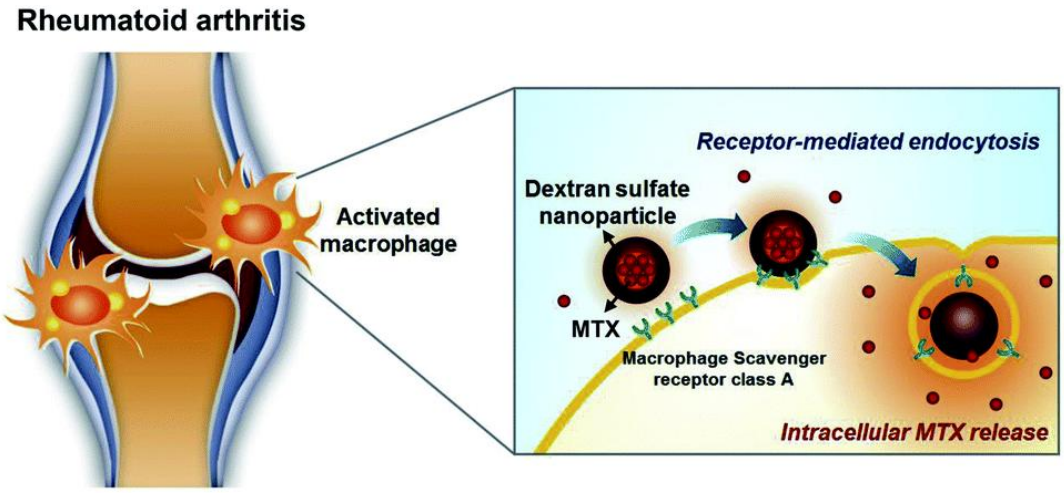

Figure 4: Action of DSNPs as nanoparticles for targeted RA therapy

Liposomes

Liposomes are spherical nanoparticles. It has doubled layered (outer layer= natural phospholipid; inner layer= water)[11]. In fig.5 due to its physical and chemical property it is not effective because drug accumulates in the water cavity or phospholipids [12]. Many researchers work on that. Polyethylene glycol (PEG) is effective hydrophilic polymer that can reduce the recognition and absorption of liposomes by reticuloendothelial system (RES), and prolong the action in systemic circulation[13,14]and reduces the inflammation of joint. Polymeric stealth liposomes used as a carrier to enhance the effect of dexamethasone in the treatment of arthritis. They used 1,2 –bis(10,12-tricosadiynoyl)-sn-glycero-3-phosphocholine(DC89PC)and (DSPE-PEG2000)to prepare liposome by thin film hydration method and PEG chains provided a stealth layer. This result shows liposomes accumulate in inflamed joint and reduce swelling.

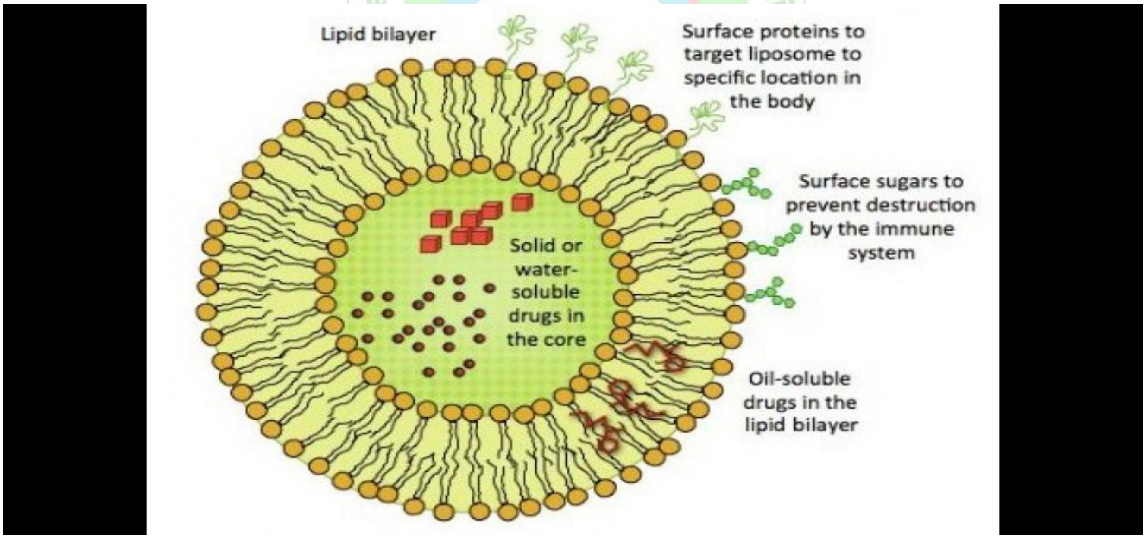

Figure 5: Structure of liposomes

Metallic nanoparticles

Metal nanoparticles have excellent properties, because it can be modified to different or multiple functional group and widely used in the field of biomedical. [15] Mostly used nanoparticles in treatment of RA is gold, cerium and iron.AU nanoparticles have an anti-angiogenesis effect, TCZ is an anti-interleukin-6(IL-6) receptor inhibitor and it can interfere with the role of IL6in pathogenesis of RA .and HA (Hyaluronate)shows protective effect on cartilage and lubrication. And complex of IL6, HA and AU formed (HA-AU NP/-TCZ) complex on RA confirmed by ELISA (enzyme-linked immunoassay), histology and western blot[15]Synthesized manganese ferrite/ceria co-decorated mesoporous silica nanoparticles (MFC-MSNs) used to treat RA In fig.6.[16] MFC-MSNs in the injection form could relieve intra articular hypoxia, inflammation and other pathological conditions. Nanoparticles have synergetic effect on scavenging reactive oxygen species (ROS) and produced O2which helps to reduce the M1 macrophages and induce M2 macrophages polarization. Monodisperse Silica nanospheres are used as a delivery carrier and enhance the therapeutic effect.

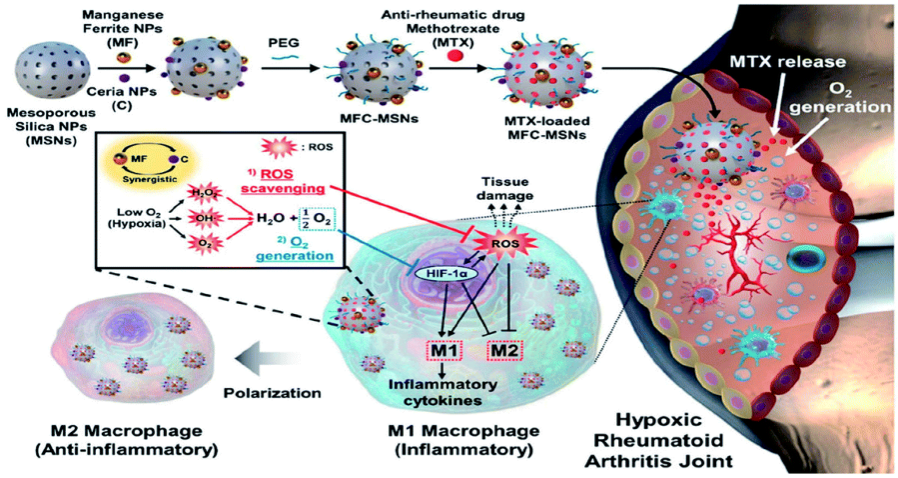

Figure 6: Mode of action of MFC-MSNs in RA treatment

Inorganic non-metallic nanomaterial

Silica is one of the inorganic non-metallic materials in fig.7 widely used in the treatment of rheumatoid arthritis[17]. (MNS-CC) plays important role. It was observed that, this nanoparticle can promote the production of HA and inhibit synovial inflammation and promote bone repair process. Mesoporous silica is first choice because of its good biocompatibility and degradability. A functional group (PEI) is added to its surface which helps delivering of (HAS2) .Treatment has long duration of action, convenient, effective and good therapeutic effect.

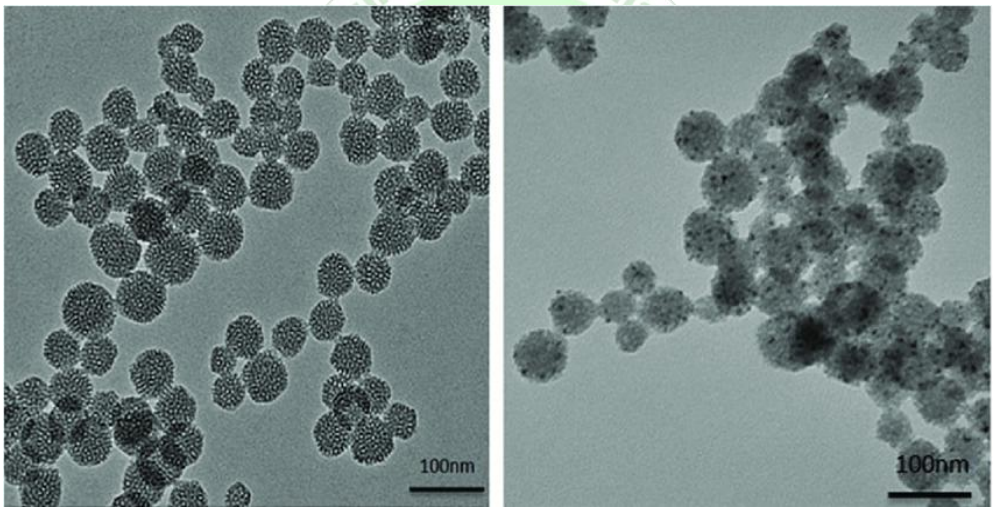

Figure 7: Structure of silica as a nanomaterial

BIONIC NANOPARTICLES:

It is also called as biomimetic, biogenesis etc.It includes nanoparticles coated with cell and exosomes encapsulated

Nanoparticles coated with cell

It is biological cell membrane mediated drug delivery system. It mechanism is very simple. This technology reduces the immunogenicity of the nanoparticles and it has more blood circulation time because nanoparticles are coated i.e. surface of the nanoparticles with the biological endogenous cell membrane (such as macrophage membrane, neutrophil membrane, red blood cell membrane etc) as a functional material.[18,19]. The nanoparticles coated with the biological cell membrane inherit the antigenic exterior and associated membrane functions of the source cells, such as chemotaxis to inflammatory sites, neutralization of cytokines. Macrophages and neutralization are important innate immune cells in the body. They are involved in the inflammatory response of the body and can cause synovium hyperplasia, secrete a variety of degrading enzymes, and cause cartilage destruction and the expression of inflammatory factors [20]. Immune cells are widely used for the biomimetic nano-drugs with anti-inflammatory properties. used macrophages-derived micro vesicle (MMV) encapsulated nanoparticles (MNP) for targeted therapy of RA. MMV membrane proteins are similar to macrophages and show similar activity. Then the poly(lactic-co-glycolic acid) (PLGA) nanoparticles were coated with MMV and tacrolimus was encapsulated in the bionic nanoparticles. The study shows that MMV can become a promising target bionic carrier for the treatment of arthritis. In fig.8.nanoparticles containing red blood cell membranes to coat polymer nanoparticles to treat RA. MMV has great future in treatment of rheumatoid arthritis

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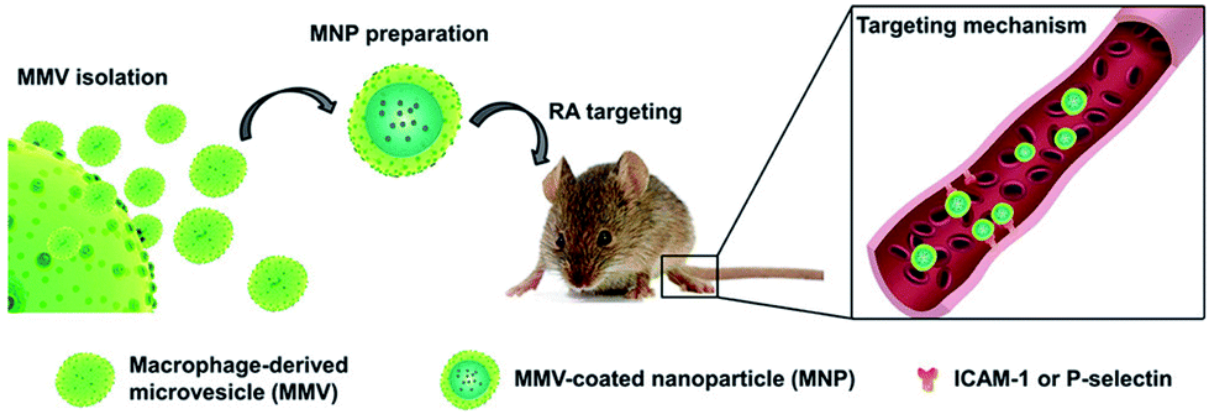

Figure 8: Action of MMV-coated nanoparticles targeting sites of RA

Exosomes encapsulated:

Exosomes are cell vesicles containing complex RNA and proteins, which can be used as drug carriers to improve biocompatibility and provide more options for personalized treatment of inflammation [21]. Nanoparticles drug delivery based on exosomes has been successfully applied to a variety of different diseases, but it is rarely used in treatment of RA. Synthesized a biomimetic exosome encapsulated with dexamethasone sodium phosphate nanoparticles is used. Later it was modified with folic acid (FA)-polyethylene glycol (PEG)-cholesterol (Chol) complex (FPC-Exo/Dex) and it target on inflammatory joints. The FPC-Exo/Dex nanoparticles can inhibit the production of pro-inflammatory cytokines and increase the expression of anti-inflammatory cytokines. [22]SPARC is new immerging treatment for rheumatoid arthritis. It has a strong affinity for albumin. Synthesized methotrexate-loaded human serum albumin nanoparticles (MTX@HSA NMS) and used them as a biomimetic drug delivery system to treat RA. infig. 9. SPARC (secreted protein complied based and rich in cysteine) biomimetic nanoparticles has great variety and provide new developing treatment for RA

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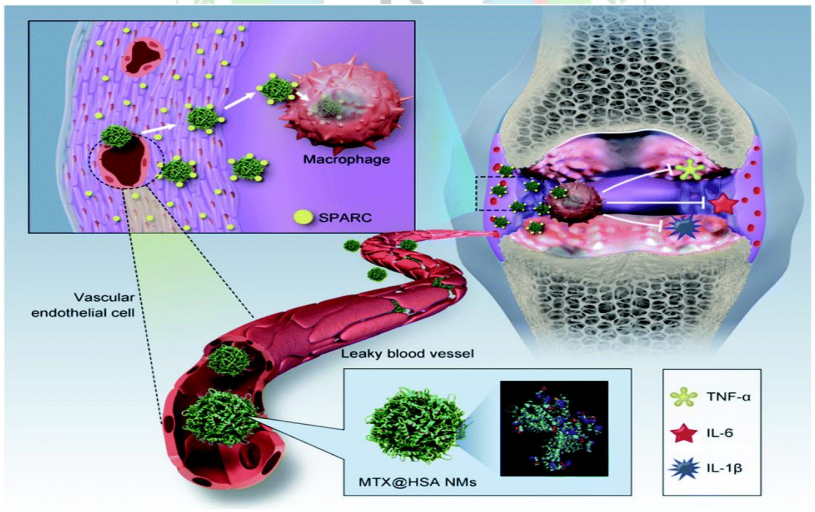

Figure 9: Delivery of methotrexate-loaded human serum albumin nanomedicines in RA

The Material Itself with Anti-Inflammatory Properties for Treatment Of Rheumatoid Arthritis

Monovalent gold has anti-inflammatory activity. Therefore the drugs which contain monovalent gold also have these properties and it is useful for treatment of rheumatoid arthritis. These anti-inflammatory properties of gold which is useful to treatment of RA discovered in 1890. But at present its application or utilization in treatment of RA is restricted because of its large number of side effects. [23].At present gold cluster has great contribution in treatment of RA with lowtoxicity.[24]synthesized gold cluster(GA) to treat RA and protect the bone. AU clusters with natural tripeptide glutathione also called as thioligand, after purification, show excellent properties such as good biocompatibility, ultra fine size and high stability they have direct biological effects without using drugs carrier. This AU clusters inhibit the differentiation and function of osteoclasts. It also prevent bone injury by inhibiting the activation of NF-KB signally pathway. Activation of osteoclast causes bone erosion. Therefore, inhibiting the activation of osteoclast pro-inflammatory cytokines and their differentiation is important method to prevent bone destruction.(This activity is observed in rats)

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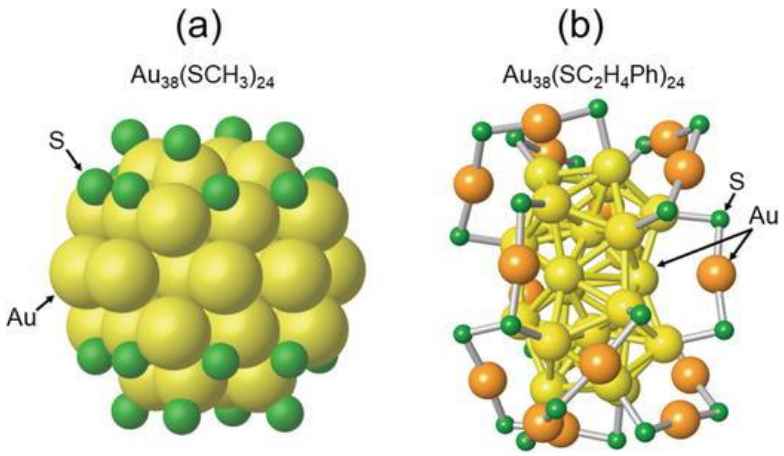

Figure 10: structure of gold cluster

Cationic nanoparticles

Cell-free DNA release from damaged or dead cells which is recognized by nucleic acid sensors (NA sensors) for example: toll-like receptors (TLR) its leads the activation of immune system and chronic inflammation which make worse condition in arthritis. The clinical study shows that the content of cell-free DNA in serum and synovial fluid of patients with rheumatoid arthritis is increased. Therefore, removing cell-free DNA can be effective in treatment of arthritis. Cationic polymers have been widely used in gene therapy as non-viral vectors of nucleic acids[23] it remove cell-free DNA (scavenging process) and inhibit the progression of arthritis. Cation have strong positive charge and contribute to systemic toxicity.

In order to reduce toxicity we use self-assembled poly(lactic-co-glycolic acid) block-poly (2-dimenthylamino) ethyl methacrylate) (PLGA-b-PDMA) copolymer to prepare cationic nanoparticles that can effectively inhibit joints inflammation, repair damaged cartilage tissue, enhance its pharmacokinetic properties, and avoid potential systemic toxicity.

If nanoparticles have more accumulation, and longer retention to the joint site (inflamed joint). So, frequency of administration alter according to condition the clinical result obtained is seen under MRI, Histology and ELISA test generally, they relive ankle swelling and bone degradation hence, have good therapeutics effect on rheumatoid arthritis. in fig.11.

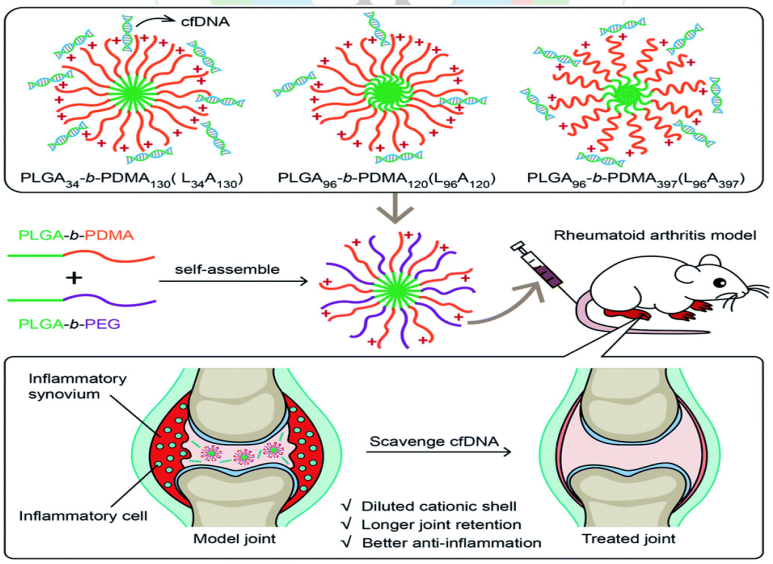

Figure 11: Cationic activity and binding of cell free DNA

CONCLUSION

Rheumatoid arthritis (RA) is chronic anti-inflammatory autoimmune disease. It mainly affects the joints and increases synovial thickness and result in swelling the different techniques or treatments are used in RA are GCS, NSAIDs but it has several side-effects; to overcome these side effects new technology comes into existence called as nanotechnology. It is a science which utilizes different types of nanoparticles/nanomaterials for effective drug delivery. It has less side effects and their accumulation at inflamed site or joint tissue reduces swelling also inflammation. They have anti-inflammatory activity. Less toxic in nature. Hence, provide greater safety to the patient. Nanoparticles are easy to synthesized and directly act one specific site. Also it has good therapeutic effect in treatment rheumatoid arthritis. It gives new direction to the treatment and development of nanoparticles. Nanotechnology has great future in treatment of RA.

Abbreviation index:

RA – rheumatoid arthritis

NSAIDs – non-steroidal anti-inflammatory drug

GCS – glucocorticoids

DMARDS – disease-modifying anti-rheumatic drug

RES – reticuloendothelial system

ROS – reactive oxygen species

HA – hyaluronate

HAS2 – hyaluronate synthase-2

SPARC – secreted protein complied-based and rich in cysteine

TLR – toll-like receptor

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