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Review on Nanoparticles, Applications and Folate Targeted Nanoparticles for Rheumatoid Arthritis Therapy

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ABSTRACT: Nanoparticles (NPs) are wide class of materials that include particulate substances, which have one dimension less than 100 nm at least. NPs are not simple molecules itself and therefore composed of three layers i.c. (a) The surface layer,(b) The shell layer, (c) The core. NPs are broadly divided into various categories depending on their morphology, size and chemical properties.NPs can be used in variety of applications in drugs and medicines, manufacturing and materials. An inflammatory condition Known as rheumatoid arthritis (RA) causes persistent joint inflammation that ultimately causes serious disability and early death. FA is a high affinity ligand for the FR, and even after derivatization via one of its carboxyl groups, folate retains a high affinity. Although the Ka of folate conjugates for FRs is higher than FA (-10x), indicating a slight reduction in the binding affinity, this is still within the nM range.

KEYWORDS: Nanoparticles,drugs and medicines,Joint inflammation , Rheumatoid arthritis, Folic Acid.

I. INTRODUCTION

Nanotechnology is a known field of research since last century. Since "nanotechnology" was presented by Nobel laureate Richard P. Feynman during his well famous 1959 lecture "There's Plenty of Room at the Bottom" (Feynman, 1960), there have been made various revolutionary developments in the field of nanotechnology. Nanotechnologyproduced materials of various types at nano scale level. Nanoparticles (NPs) are wide class of materials that include particulate substances, which have one dimension less than 100 nm at least. Depending on the overall shape these materials can be OD, ID, 2D or 3D. Theimportance of these materials realized when researchers found that size can influence the physio-chemical properties of a substance e.g. the optical properties. A 20- nm gold (Au), platinum (Pt), silver (Ag), and palladium (Pd) NPs have characteristic wine red color, yellowish gray, black and dark black colors, respectively. Fig. 1 shows an example of this illustration, in which Au NPs synthesized with different sizes. These NPs showed characteristic colors and properties with the variation of size and shape, which can be utilized in bioimaging applications. As Fig. 1 indicates, the color of the solution changes due to variation in aspect ratio, nanoshell thickness and % gold concentration.

The alteration of any of the above discussed factor influences the absorption properties of the NPs and hence different absorption colors are observed.[1,2,3]

NPs are not simple molecules itself and therefore composed of three layers i.c. (a) The surface layer, which may be functionalized with a variety of small molecules, metal ions, surfactants and polymers. (b) The shell layer, which is chemically different material from the core in all aspects, and (c) The core, which is essentially the central portion of the NP and usually refers the NP itself. Owing to such exceptional characteristics, these materials got immense interest of researchers in multidisciplinary fields. [4,5,6]

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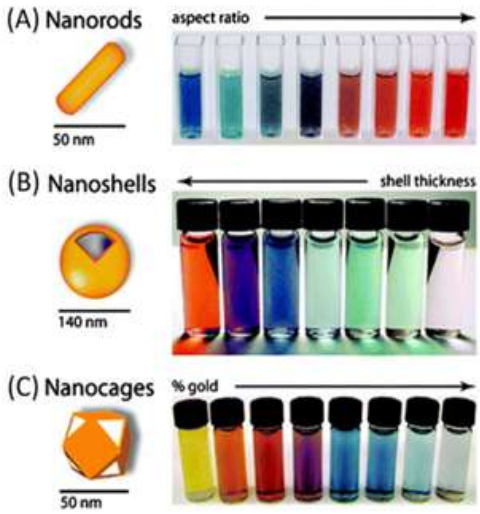

Fig:1 Colour dependence of Au NPs on size and shape.

II. CLASSIFICATION

NPs are broadly divided into various categories depending on their morphology, size and chemical properties. Based on physical and chemical characteristics, some of the well-known classes of NPs are given as below,

- Carbon-based NPs

Fullerenes and carbon nanotubes (CNTs) represent two major classes of carbon-based NPs. Fullerenes contain nanomaterial that are made of globular hollow cage such as allotropic forms of carbon. [7,8,9]

- Metal NPs

Metal NPs are purely made of the metals precursors. Due to well-known localized surface plasmon resonance (LSPR) characteristics, these NPs possess unique optoelectrical properties. NPs of the alkali and noble metals Le. Cu, Ag and Au have a broad absorption band in the visible zone of the electromagnetic solar spectrum. The facet, size and shape controlled synthesis of metal NPs is important in present day cutting-edge materials. [10]

- Ceramics NPs

Ceramics NPs are inorganic nonmetallic solids, synthesized via heat and successive cooling. They can be found in amorphous, polycrystalline, dense, porous or hollow forms. Therefore, these NPs are getting great attention of researchers due to their use in applications such as catalysis, photocatalysis, photodegradation of dyes, and imaging applications.[11]

- Semiconductor NPs

Semiconductor materials possess properties between metals and nonmetals and therefore they found various applications in the literature due to this property. Semiconductor NPs possess wide bandgaps and therefore showed significant alteration in their properties with bandgap tuning. Therefore, they are very important materials in photocatalysis, photo optics and electronic devices (Sun, 2000). As an example, variety of semiconductor NPs are found exceptionally efficient in water splitting applications, due to their suitable bandgap and bandedge positions. [12]

- Polymeric NPs

These are normally organic based NPs and in the literature a special term polymer nanoparticle (PNP) collective used for it. They are mostly nanospheres or nanocapsular shaped. The former are matrix particles whose overall mass is generally solid and the other molecules are adsorbed at the outer boundary of the spherical surface. In the latter case the solid mass is encapsulated within the particle completely. The PNPs are readily functionalize and thus find bundles of applications in the Literature.[13,14]

III. APPLICATIONS

NPs can be used in variety of applications. Some important of these are given below

- Applications in drugs and medications:

Nano-sized inorganic particles of either simple or complex nature, display unique, physical and chemical properties and represent an increasingly important material in the development of novel nanodevices which can be used in numerous physical, biological, biomedical and pharmaceutical applications. NPs have drawn increasing interest from every branch of medicine for their ability to deliver drugs in the optimum dosage range often resulting in increased therapeutic efficiency of the drugs, weakened side effects and improved patient compliance.The selection of NPs for achieving efficient contrast for biological and cell imaging applications as well as for photo thermal therapeutic applications is based on the optical properties of NPs. [15,16]

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- Applications in manufacturing and materials:

Nanocrystalline materials provide very interesting substances for material science since their properties deviate from respective bulk material in a size dependent manner. Manufacture NPs display physicochemical characteristics that induce unique electrical, mechanical, optical and imaging properties that are extremely looked-for in certain applications within the medical, commercial, and ecological sectors The potential benefits of nanotechnology have been documented by many manufacturer at high and low level and marketable products are already being mass-produced such as microelectronics, aero-

Space and pharmaceutical industries. Among the nanotechnology consumer products to date, health fitness products from the largest category, followed by the electronic and computer category as well as home and garden category.[17]

- Applications in the environment:

Most of environmental applications of nanotechnology fall into three categories:
Environmentally benign sustainable products (e.g. Green chemistry or pollution prevention).
Remediation of materials contaminated with hazardous substances.
Sensors for environmental stages. [18]

- Applications in electronics:

There has been growing interest in the development of printed electronics in last few years because printed electronics offer attractive to traditional silicon techniques and the potential for low cost, large area electronics for flexible displays, sensors. Printed electronics with various functional inks containing NPs such as metallic NPs, organic electronic molecules, CNTs and ceramics NPs have been expected to flow rapidly as a mass production process for new types of electronic equipment. [19]

- Applications in energy harvesting

Recent studies warned us about the limitations and scarcity of fossil fuels in coming years due to their nonrenewable nature. Therefore, scientists shifting their research strategies to generate renewable energies from easily available resources at cheap cost. They found that NPs are the best candidate for this purpose due to their, large surface area, optical behavior and catalytic nature. Especially in photocatalytic applications, NPs are widely used to generate energy from photoelectrochemical (PEC) and electrochemical water splitting. [20]

- Applications in mechanical industries:

As revealed from their mechanical properties through excellent young modulus, stress and strain properties, NPs can offer many applications in mechanical industries especially in coating, lubricants and adhesive applications. Besides, this property can be useful to achieve mechanically stronger nanodevices for various purposes. Tribological properties can be controlled at nanoscale level by embedding NPs in the metal and polymer matrix to increase their mechanical strengths. It is because, the rolling mode of NPs in the lubricated contact area could provide very low friction and wear. In addition, NPs offer good sliding and delamination properties, which could also effect in low friction and wear, and hence increase lubrication effect.[21]

IV. NANOPARTICLES FOR RHEUMATOID ARTHRITIS THERAPY

Rheumatoid arthritis:

An inflammatory condition Known as rheumatoid arthritis (RA) causes persistent joint inflammation that ultimately causes serious disability and carly death. Chronic synovial membrane inflammation brought on by RA advances to extra-articular disease symptoms, including peri articular bone erosion, articular cartilage degradation, and irreversible abnormalities. Aging is among the main risk factors for the development of RA. According to estimates, RA affects 1% of people worldwide and women are 2-3 times more likely than males to have the disease. India has a prevalence of RA between 0.28% and 0.7%, comparable to that of affluent countries. RA can affect people of any age, although it is most common in those between the ages of 30 and 50 RA may impact any joint in the body. However, it mostly impacts the wrist and knee joints' proximal interphalangeal, metacarpophalangeal, and metatarsophalangeal joints. The wrist is the area of RA most frequently afflicted. It has also been noted that there are some variances in the predominance of swelling and soreness, with swelling more common in tiny joints like the metacarpophalangeal joints and discomfort more common in major joints like the elbow, shoulder, and knee.[22,23]

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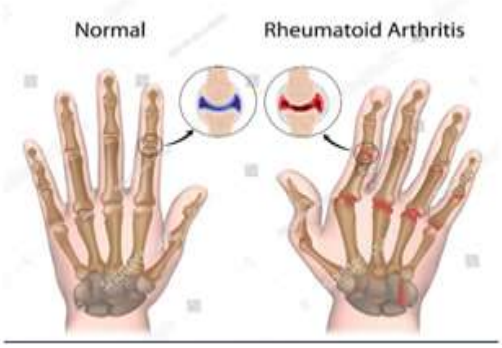

Rheumatoid Arthritis in Hand

Novel Drug Delivery Systems in RA Management:

The traditional drug administration methods have benefits and drawbacks, including limited solubility and permeability, poor bioavailability, Gl enzyme degradation, first-pass metabolism, food interactions, high dosage requirements, and related drug toxicity. Numerous studies have been conducted to address these drawbacks, which has resulted in the development of innovative drug delivery methods (NDDS). These cutting-edge systems have target-specific efficacy, are needed in lower dosages, have less hazardous side effects, high solubility and permeability, and improve bioavailability. [24]

- Chemotherapeutic Dual Drug Delivery:

Son and colleagues created viscous emulsions comprising MTX-loaded hyaluronic acid (Met- HA), dexamethasone-loaded microcapsules (Dex-M), and Dex-M distributed inside of Met-HA, and then injected these formulations into articular joints to create drug depots. When Met-HA and Dex-M were injected together, it was shown that the rate of RA repair was quicker than when they were injected separately. Thus, it was determined that using two drugs at once had a long-lasting synergistic impact that improved RA healing. [25]

- Emulgels:

Nimesulide emulsion was incorporated into an Aloe vera gel basis to create the nimesulide- Aloe vera transemulgel (NAE), which was then subjected to in-vitro testing and in-vivo anti-inflammatory evaluation. The produced emulgels were assessed for stability, pH, viscosity, in-vitro permeation and skin irritation. [26]

- Folate-conjugated Albumin Nanoparticles:

Folic acid-etoricoxib-bovine serum albumin nanoparticles (F-ETX-NPs) were created by Bilthariya et al. They demonstrated increased bioavailability and a stronger retention potential of the nanoparticles towards activated macrophage cells. The technique may thus be a useful therapeutic alternative to reduce medication dosage and improve biocompatibility, it was determined. [27]

- Folate Coupled Dendrimer:

Intending to deliver the medication to specific locations to alleviate inflammation and examine its biodistribution pattern in arthritic rats, Chandrasekar prepared folate-targetedPolyethylene glycol (PEG) conjugates of anionic G3.5 poly (amido amine) (PAMAM) dendrimer. Scientists created indomethacin-loaded folate-PEG-PAMAM conjugates by a carbodiimide-mediated coupling process in this work. Folate-PEG conjugation boosted the drug loading efficiency 10- to 20-fold, and it was discovered that the drug release in-vitro was regulated. Due to noticeably lower absorption of the conjugates by the stomach, authors found little adverse effects associated with the stomach. The total drug targeting efficiency (TE) for the folate-PEG conjugate was determined to be 3.44 in comparison to the natural dendrimer (Te-1.72). The authors concluded that folate-PEG-PAMAM conjugates could be the best option for the effective, side-effect-free administration of medications to inflammation. [28]

- Lipid-based Vesicular Nanocargoes:

Because of their adaptability and capacity to hold several drugs, lipid nano-vesicular carriers, including ethosomes, liposomes and niosomes are some of the most recent developments in the treatment of RA. They have had notable effects in RA treatment, allowing for dosage reduction and improved drug localisation via active and passive drug targeting.

- Microspheres

Pectin-based colon-specific microspheres (multiparticulate delivery system) were created by Ramasamy et al. Using an emulsion dehydration process. Eudragit $100 was applied to the microspheres using the solvent evaporation technique. The authors examined the influence of variables including emulsifier, stirring time/speed, and polymer on surface morphology, size, in-vitro release, entrapment effectiveness, and in-vivo performance. Studies conducted in-vivo revealed that medication at a steady therapeutic dose for 24 hr had a strong anti-inflammatory impact. Based on

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their research, the scientists concluded that eudragit-coated pectin microspheres might be useful for aceclofenac administration to the colon in the chronopharmacological therapy of RA.[29]

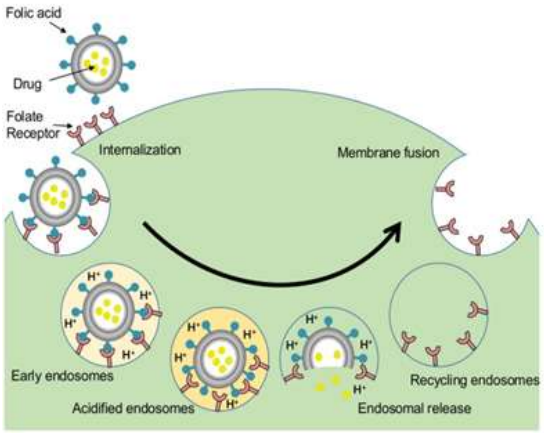
V. FOLATE TARGETED NANOPARTICLES FOR RHEUMATOID ARTHRITIS:

Folate receptor:

Prolonged inflammatory states may last for weeks, months or even years. Macrophages can display different markers of activation and maturation depending on the type of activation, the immune cells involved, state of differentiation, type of aggression and the tissue where this all takes place. FRB, whose expression is selectively elevated in RA synovial macrophages, has been used as a target for immunotherapy in a number of clinical situations, such as autoimmunity and chronic inflammation. FRs include at least four isoforms, a, and exhibiting distinct patterns of tissue expression. FR alpha is expressed at the luminal surface of polarized epithelial cells of normal adult tissues including proximal kidney tubules, uterus, fallopian tube, choroid plexus, epididymis, submandibular salivary, acinar cells of the breast, bronchial gland, type I and type II pneumocytes in the lung, and trophoblasts of the placenta. In turn, FRBeta is a differentiation marker in the myelomonocytic lineage during (C neutrophil maturation and is amplified in activated monocytes and macrophages. However, FR beta in neutrophils is unable to bind the vitamin FA (or folate) due to dysfunctional posttranslational modifications. In contrast, a functional FRB with nanomolar affinity for folate has been identified on activated macrophages, key effect cells in chronic inflammatory diseases such as RA, atherosclerosis, systemic lupus erythematosus, Crohn's disease and osteoarthritis. FR gamma has been detected in normal and malignant hematopoietic cells present in the spleen, bone marrow and thymus, as well as ovarian, cervical and uterine carcinoma. A polymorphism in the FR gamma gene is caused by a mutation that results in a carboxyl-terminal truncation of the protein; the mutated protein is referred to as FR gamma. [30-41]

Folate mediated targeting:

FA is a high affinity ligand for the FR, and even after derivatization via one of its carboxyl groups, folate retains a high affinity. Although the Ka of folate conjugates for FRs is higher than FA (-10x), indicating a slight reduction in the binding affinity, this is still within the nM range. FRs mediate cellular internalization of folate conjugates via receptor-mediated endocytosis. In this way, folate conjugation constitutes a valid method for targeted delivery of therapeutic agents to FR expressing cells. Receptor-mediated endocytosis of folate conjugates occurs through a succession of distinct steps,beginning with conjugate binding to a cell surface FR. As a GPI anchored protein, FR internalization is thought to use clathrin independent carriers (CLIC) and GPI-anchored protein-enriched early endosomal compartment (GEEC) pathway. After membrane invagination and internalization to form an endocytic vesicle, the pH of the vesicle lumen decreases through the action of proton pumps localized in the endosome membrane. This acidification mediates a conformational change in the FR protein allowing the release of bound ligand and its delivery in the cytosol. Finally, the FR recycles back to the cell surface, allowing the delivery of additional folate conjugates into the cell. Besides their high affinity for its receptor, other properties make FA an attractive ligand for use in drug targeting. These features include its convenient availability, low molecular weight, easy conjugation chemistry, lack of immunogenicity, water solubility, stability in diverse solvents, pH and temperature.



Schematic representation of folate mediated endocytosis

Furthermore, the small size of the folate ligand also allows good tissue penetration and rapid clearance from receptor negative tissues. Therefore, these desirable properties render folate as one of the most studied ligands in targeted drug delivery. A wide range of molecules and drug carriers have been conjugated to folate and tested in FR targeting.[42,43,44]

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Current RA therapy:

The treatment of RA in the last years is characterized by a firm evolution of new agents and new approaches. Progress in knowledge about cellular and molecular mechanisms of RA and the development of new therapies have changed the overview of scientific community about RA. Discoveries concerning its pathogenesis have led to the development of new agents with specific molecular targets, which have transformed the prognosis for numerous RA patients. Treatment paradigms in RA have shifted dramatically from controlling symptoms (using nonsteroidal anti-inflammatory drugs, NSAIDs, and corticosteroids) for controlling the disease process with the suppression of inflammation (disease-modifying antirheumatic drugs, DMARDs, and biologics), in order to prevent joint damage. These changes in RA management result from growing evidences suggesting that early RA identification and treatment with DMARDs leads to improved prognosis and outcomes. Therefore the aims in RA management besides disease remission also inchide an improved functional status. The new criteria for the classification/diagnosis of RA proposed in 2010 reflect a probabilistic method to RA diagnosis and are specifically useful before the erosions that are typical of RA become detectable on X-rays. They include four scored areas: symptom duration (<or>6 weeks), number and type of joints involved, biomarkers of inflammation (acute-phase reactants), and biomarkers of specific autoimmunity (RF and ACPA).

Methotrexate (MTX) is the first line therapy indicated for the treatment of RA, but other options include leflunomide, sulfasalazine, and hydroxychloroquine. MTX is an analogue of folate and, hence, has structural and physiochemical properties considerably similar to those of folate, it has two carboxyl groups in its molecule and both of them are most completely dissociated in the physiological conditions. The mechanisms proposed to explain the effects of MTX include (1) inhibition of proliferation of the inflammatory synovial cells due to inhibition of purine and pyrimidine synthesis; (ii) inhibition of the synthesis of polyamines; (iii) changes in cellular redox state and reduction in intracellular glutathione levels, leading to decreased macrophage and lymphocyte recruitment function and increasedApoptosis sensitivity, and (iv) inhibition of the enzyme aminoimidazolecarboxamide. Ribonucleotide (AICAR) transformylase.consequent elevation of AICAR cellular levels, resultinginhibition of AMP deaminase and ultimately leading to an increase in extracellular adenosine levels.

Patients receiving MTX therapy should be reexamined after 3 months of therapy for symptomatic improvement. However, the toxicity associated with MTX administration can be minimized if it is dosed correctly and monitored appropriately. Major toxic effects, such as hepatic, pulmonary, renal and bone marrow abnormalities, require careful monitoring. Minor toxic effects, such as stomatitis, malaise, nausea, diarrhea, headaches and mild alopecia, are common but respond to folate supplementation. Other effects include gastrointestinal or bone marrow toxicity, pneumonitis,

Hepatotoxicity and cirrhosis. If patients are MTX intolerant or have moderate or high disease activity after 3 to 6 months of therapy another DMARD should be used or added, or alternatively biologic agents. In RA therapy biological agents used are anti-TNF-a molecules, responsible for the neutralization of TNF-a, the master regulator of RA immunopathogenesis. Anti-TNF-a agents fall into three structural categories: anti-TNF-a IgG antibodies (the monoclonal antibodies) (mAbs) infliximab, adalimumab, and golimumab), PEGylated Fab' fragments (certolizumab), and modified TNF-R2 receptors (etanercept). Furthermore, biological agents include an inhibitor of T-cell costimulation (fusion protein composed of the Fe region of the immunoglobulin IgG1 fused to the extracellular domain of CTLA-4, abatacept), an agent leading to B-cell depletion (chimeric monoclonal antibody against the protein CD20, rituximab) and the II.-6 receptor (IL-6R)-blocking monoclonal antibody (tocilizumab), as well as the IL-1 inhibitor (anakinra).

The implementation of these effective biological agents has been accompanied by ongoing health economic discussions regarding the implementation of these highly effective, but accordingly, highly priced drugs in the standard treatment guidelines of rheumatic diseases. Despite their high clinical effectiveness, the cost efficacy of biologicals is questionable bearing in mind that this therapy costs are 20-200 fold compared to traditional DMARDs.[45-55]

VI. CONCLUSION

The fact that is particularly important in Rheumatoid Arthritis, where the first line therapy, MTX, presents several side effects, as potential toxicity and possible depression of the bone

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marrow or leading to hepatitis and liver function. Moreover, if patients are MTX intolerant another DMARD should be used or added, or alternatively biologic agents. However, the development of biological substances for the treatment of rheumatic conditions has been accompanied by ongoing health economic discussions regarding the implementation of these highly effective, but accordingly, highly priced drugs in the standard treatment guidelines of rheumatic diseases. In this way, the recent strategies of folate-targeted nanoparticles with MTX were effective to improve inflammatory disease treatments while decreasing the MTX side effects with an improved cost-benefit ratio.

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