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A Review on: Overview of Rheumatoid arthritis and nanotechnology, alongside recently developed nanomedicine for the disorders.

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ABSTRACT:

Emerging drug delivery methods including liposomes, microspheres, nanoparticles, dendrimers, and transdermal delivery have a lot of assurance. For the treatment of rheumatoid arthritis Nanomedicines are very effective and lowest side effects. Rheumatoid arthritis (RA) is an autoimmune disorder that is characterized by persistent joint inflammation that causes significant disability and early death. Nanomaterials have irreplaceable advantages. The nanomaterials have shown great application prospects in the treatment of rheumatoid arthritis. Various nanocarriers shows the excellent effect in the treatment of Rheumatoid arthritis like nanoparticles, nanosponges, liposomes, noisome etc. Nanomaterials can increase bioavailability and specifically target damaged joint tissue in the treatment of RA. In this review, we summarized the development of nanomaterials' use in the treatment of rheumatoid arthritis and various Non-steroidal Anti-inflammatory drug used in treatment of Rhumatoid Arthritis.

KEYWORDS: Rheumatoid Arthritis, Inflammation, NSAIDS, Nanocarrier

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1. INTRODUCTION:

A chronic autoimmune inflammatory condition known as rheumatoid arthritis (RA) is characterised by synovial membrane inflammation, which causes articular cartilage to gradually break down, the hardening of the bone, and other abnormalities.[1]0.24% to 1% of the world's population suffers from the common auto immune illness rheumatoid arthritis (RA). The inflammatory response in RA patients produces sensations of pain, edema, strength, and decreased joint mobility, which, if not treated, can progress to a serious condition.[2]

Rheumatoid Arthritis is marked by inflammation of the synovium, which leads to pannus development. As different pro-inflammatory mediators invade the joints, they cause inflammation that leads to cartilage damage and bone loss, which ultimately cause RA.Fibroblasts, macrophages, lymphocytes, pro-inflammatory cytokines, prostaglandins, and enzymes are the most crucial mediators that are crucial to the process of inflammation.B cells, T cells, and macrophages are responsible for the immune response in RA.[3]

The use of nanotechnology in the treatment of numerous inflammatory conditions is currently on the rise. In terms of medical and biological research, it has generated a wide range of tools, including target drug delivery systems, several types of implants, and countless types of diagnostic tools for the detection of various illnesses. When a drug is specifically targeted with nanomedicines, its pharmacokinetics and pharmacodynamics are enhanced while its lethality is decreased. When compared to currently available medications, nanomedicines provide a number of benefits, including enhanced lipophilic drug transport, decreased lethality, selective targeting, regulated drug release, and protection from drug deterioration in the body. The use of nanotechnology that is widely used in RA is nanomedicines, which comprise a variety of forms such as dendrimers, solid lipid nanoparticles, liposomes, niosomes, transferosomes, nano-sponges, nanogels, etc. Hence, in this review, we examine the connection between rheumatoid arthritis and nanotechnology as well as recently developed nanomedicines for thedisease.[3]

1.1*Pathogenesis of Rheumatoid Arthritis:*

Rheumatoid arthritis patients generate antibodies to citrullinated protein molecules. It is an amino acid that is formed following modification after translation by peptide arginine deaminases. Anti-citrullinated protein antibodies (ACPA) are the name given to these antibodies. Complement activation is caused by antibody contact with proteins. Seropositive inflammatory disease (RA) is characterized by

the presence of antibodies.ACPA antibodies can be found in the bloodstream up to ten years before clinical signs occur.Immune cells such as innate immunity cells and adaptive immunity cells, B cells, and plasma cells enter the joint fluid in the case of rheumatoid arthritis.TNF, IL-6, and granulocyte-monocyte colony stimulating factors are cytokines and chemokines that activate endothelial cells and recruit immune cells to the synovial compartment.Rheumatoid arthritis is distinguished by bone breakdown, which is produced by osteoclast development, which is stimulated by fibroblast and inflammatory cells. The mechanism underlying environment-triggered RA is assumed to involve repeated activation of innate immunity. Smoking a cigarette promotes the formation of peptidyl arginine deaminase (PAD) in macrophages in the alveolar space, resulting in arginine conversion to citrulline in the airway. This procedure produces a " neoantigen " that initiates an immuneresponse and leads to development of antibodies anti-citrullinated proteins (ACPAs). A second environmental trigger is thought to be necessary for a disease to manifest clinically. An inflammatory process that is harmful starts once this is established. Joint injury develops over time as a result of the migration of fibroblast-like synoviocytes (FLS). Manyanti-inflammatory classes are availablefor treatment of Rheumatoid arthritislike diclofenac,Ibuprofen, ketoprofen, naproxen but flurbiprofen, Tenoxicam, Lornoxicam etc. are given bestactivitywhenusedtopically.[4]

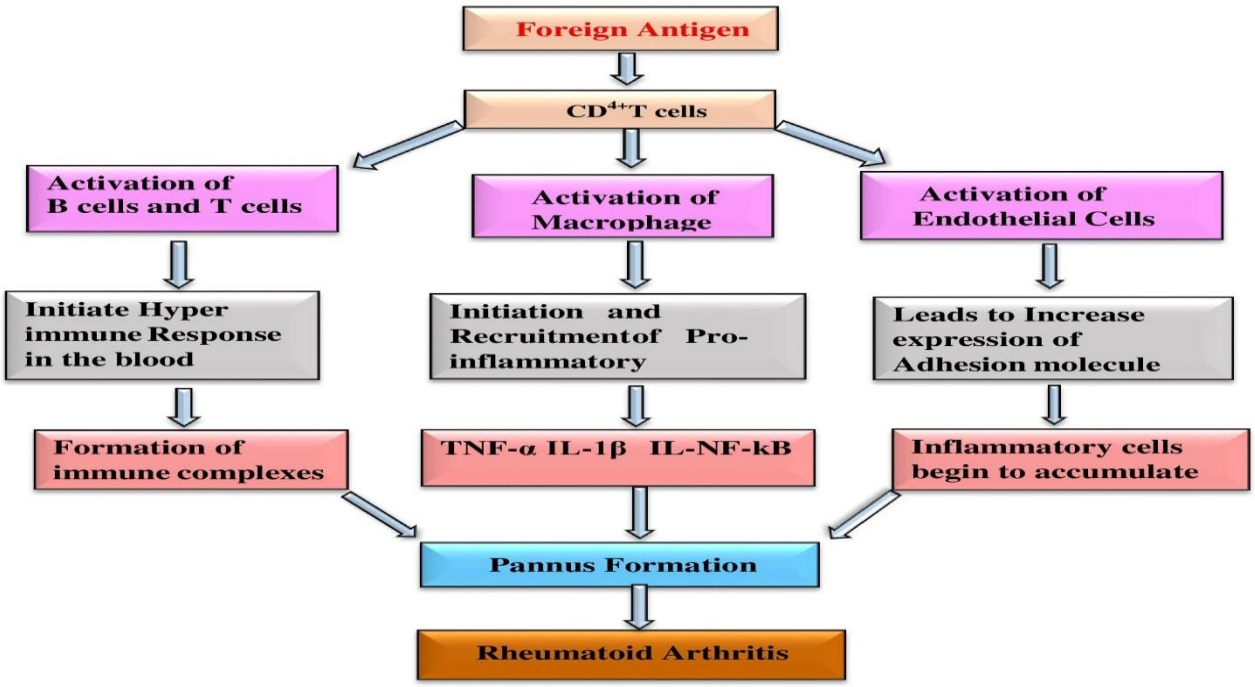


Fig.1 Pathogenesis of Rheumatoid Arthritis

1.2 Rheumatoid Arthritis Symptoms Include The Following:

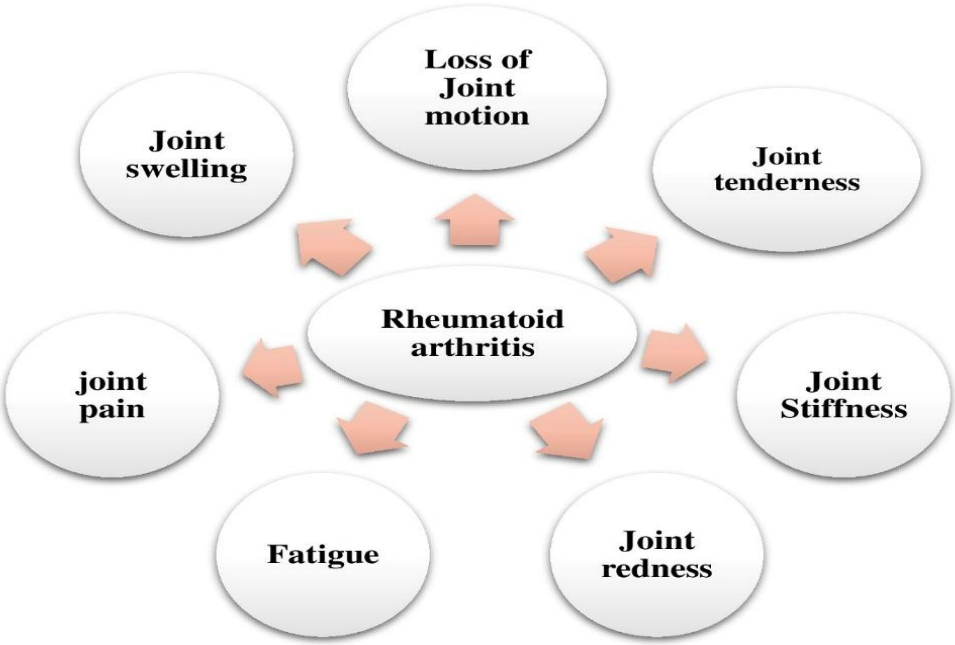


Fig.2 Symptoms Associated with Rheumatoid Arthritis

1.3 The need for new nanocarriers in rheumatoid arthritis:

In order to maintain a successful and regular active lifestyle, it is essential to diagnose RA at an early stage and detect its earliest stages.[6,7] Conventional drug delivery methods have benefits as well as drawbacks, including inadequate bioavailability, limited solubility and permeability, dietary interactions, first pass metabolism, large dose requirements, and related drug toxicity. Many research investigations have been conducted to tackle these drawbacks, resulting in the development of novel ways to deliver drugs. These innovative approaches are target-specific, need less dosages, have lower toxicity risks, high solubility and permeability, and have enhanced bioavailability.[8]Traditional RA therapy options mostly comprise the use of first-line medicines such as NSAIDs, which are nonsteroidal anti-inflammatory drugs, and steroid medications (GCs), which are primarily used to suppress painful sensations.[9]Indomethacin, celecoxib, etoricoxib, meloxicam, and other NSAIDs work by blocking the inflammatory COX enzyme.[10]

However, prolonged intake of NSAIDs may result in nephrotoxicity, high blood pressure, heart a ttack, gastro-intestinal bleeding, and ulceration.[11]Transdermal medicine distribution via the dermal route, which is safe and patient-friendly due to its simplicity, has grown in popularity in recent years. Furthermore, The cutaneous route of drug delivery includes advantages such as longer action, higher dose capacity, less adverse reactions, the ability to avoid hepatic metabolism during the first pass, and defence against medication inactivation by gastro-intestinal pH and catalysts.[1]

As illustrated in Fig. 3, this review examines new drug delivery techniques such as vesicular networks and lipid-based nanoparticulate transporters. Solid lipid nanoparticles and nanoemulsions are examples of lipophilic carriers. Liposomes, ethosomes, and niosomes are examples of vesicular systems.

2. EMERGING NANOCARRIERS USED IN MANAGEMENT OF RHEUMATOID ARTHRITIS:

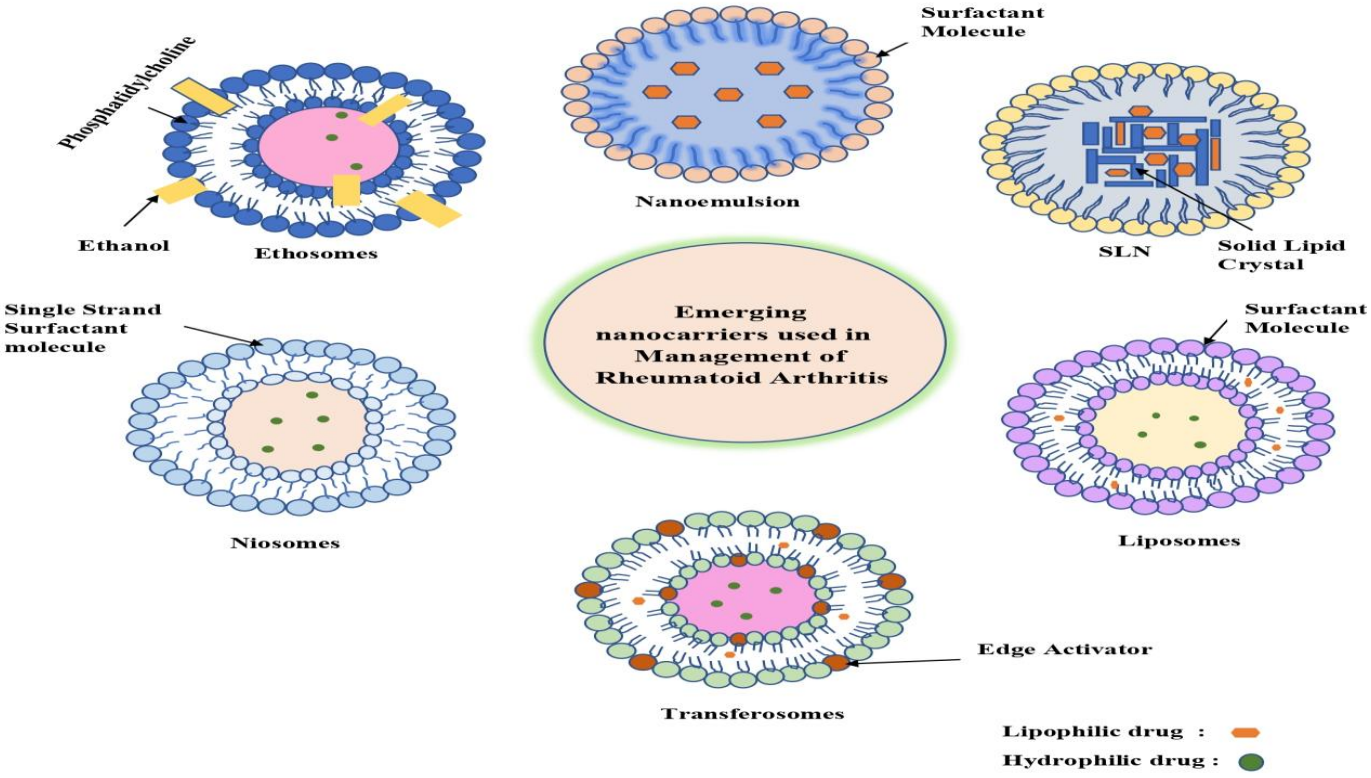


Fig.3.Emerging Nanocarriers used in Management of Rheumatoid Arthritis

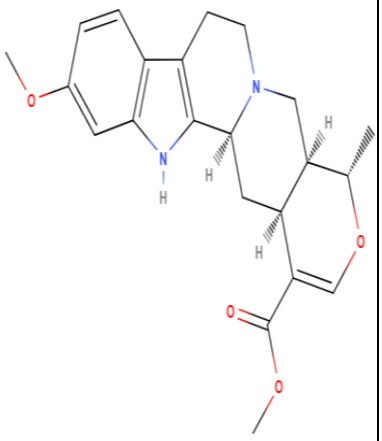
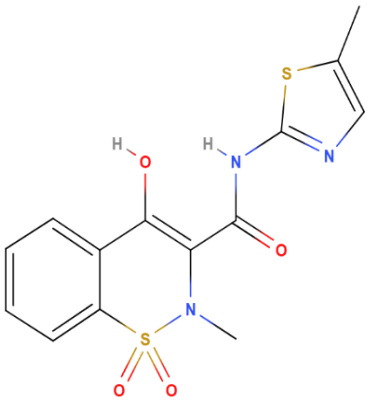
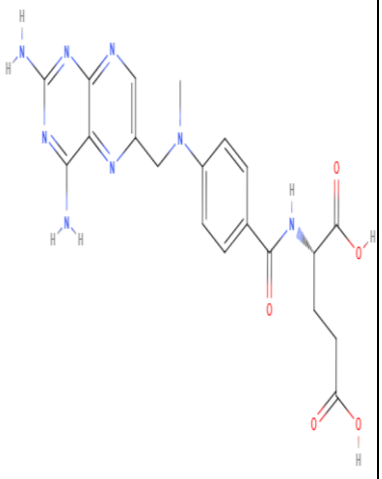
2.1 *Various Novel Nanocarriers Used In Management Of Rheumatoid Arthritis:*

2.2.1 Nano emulsion:

The average diameter of nanoemulsions, which have an isotropic, transparent composition of oil, water, and an emulsifier, can range from 20 to 500 nm. Emulsifying agents are vital for the settling of nano-emulsions due to steric resistance and repulsive electrostatic forces. The broadening of an emulsifier is required for the formation of smaller-sized droplet because it minimizes tension at the interface and energy on the surface per unit range across the emulsion's water and oil contents.[12]

Most anti-inflammatory drugs bioavailability and efficacy have been reported to be increased by nanoemulsions.[13]NEs are utilised as medication transporters, notably for less soluble and less permeable medications like MLX, EXB, and CLX, which enhance stability and loading of drugs, thus improving the absorption of drugs.[14]They quickly penetrate the rough surface of the skin due to their tiny size, raising medicine penetration.[15] NEs are distinguished by their electrical conductivity, viscosity, zeta potential , and particle size. The size of the particles is examined using freeze-fracture transmission electron microscopy, and the uniformity of the dispersion is assessed using the polydispersity index. Viscosity is a crucial component for both medication release and stability. Viscosity is determined with a cone and plate rheometers. Using electrical conductivity, the outer phase can be identified. Oil is the outer phase when the conductivity is low, whereas water is the outer phase when the conductivity is high.[16]

Table No 1. " Rheumatoid Arthritis Medications Based On Nanoemulsions"

Sr .No	Name of Drug	Nanocarrier	Particle size (nm)/Zeta energy (mV)	Beneficial Outcome	Structure	References
1.	Pubescens oil	PEG	200/	Anti-rheumatic and reducing inflammation		18
2..	Mobic	Labrafil 1944CS	60.6 - 195/–	anti-rheumatic and anti-arthritic effects		17
3.	Methotrexate	Lipoprotein	-	Anti-inflammatory effects		19

2.2.2 Solid Lipid Nanoparticle:

The benefits of nanoparticles made of polymers and oil-in-water emulsions are combined in solid nanoparticles of lipid (SLNs), colloidal transporters ranging in particle size in range of 200 nm that are often used for controlled delivery of drugs.[20]Researchers in this subject are currently interested in lipid components such as tiny emulsion, nanostructured lipid carriers, and lipid-drug mixtures. Furthermore, solid lipid nanoparticles (SLNs), which have been produced, have the potential to increase the application to the skin of hydrophilic and lipophilic medications when in contrast with others traditional carriers.[21,22]SLNs have outstanding characteristics such as good tolerability, shielding incorporated active compounds from deterioration by chemicals, increased absorption with the incorporation of both lipophilic and water-loving medications, enhanced drug-absorbing capacity, and are generally safe for biological usage.[23]SLNs are frequently eliminated from the circulation by the system of reticuloendothelial cells due to its unique size range.The lipids in SLNs were physiological lipids like cholesterol, phospholipids, and mono-, di-, and triglycerides. A variety of processes can be used to create solid lipid nanoparticles, including extreme shear mixing, ultrasonic, elevated pressure uniformity, hot homogenization, cold homogenizing, solvent emulsification, and loss of moisture processes.More emphasis has been focused on current years on lipid-based formulations in order to boost oral absorption of drugs that aren't very water-soluble by using SLNs.[24]Surfactants around a fat core with an extreme melting point to produce SLNs.In some circumstances, hydrophilic polymers are also applied to SLNs to enhance their colloidal stability.Three models of drug integration into solid lipid nanoparticles that are dependent on their production process have been reported, and each is detailed in Table 2. These include the Model of solid solution, model with a core and a shell (drug-enriched core), and the core-shell model (drug-enriched shell).[25]

Table No2. "Three models of SLN drug incorporation"

Model of solid solution	Model with a core and a shell (drug-enriched shell)	Core-shell model (drug-enriched core)
This model was developed using the cold homogenization method.	This model was created using the hot homogenization method.	The medication, which is dissolved in the lipid, becomes supersaturated as a consequence of dispersion cooling.
Drug distributed in a lipid matrix	The drug is redistributed to the lipid phase as a result of cooling the final dispersion.	At last, an additional cooling caused the lipid to recrystallize.
The correlation between lipids and medication is crucial.	Drug concentration in the surrounding membrane	emergence of a core enriched in drugs
There was no use of a drug-solubilizing surfactant.	At lipid recrystallization temperature, lipid core formation occurs.	Precipitation of medication in melting lipid

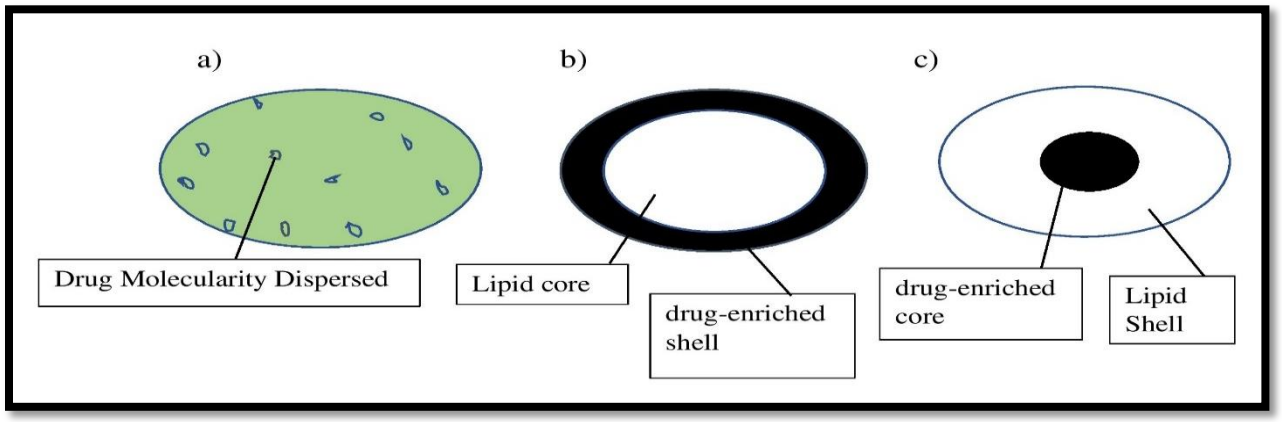
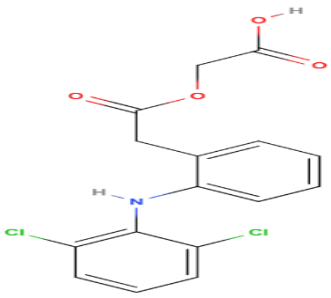
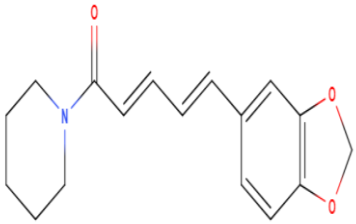
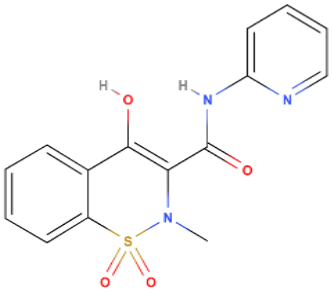
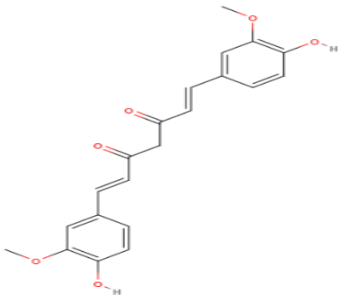


Figure 4. SLN drug incorporation models are shown schematically. The models are as follows: a) solid solution model; b) core-shell model; and c) core-shell model

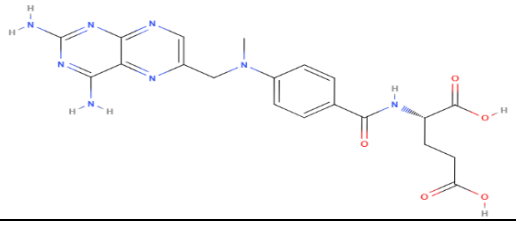
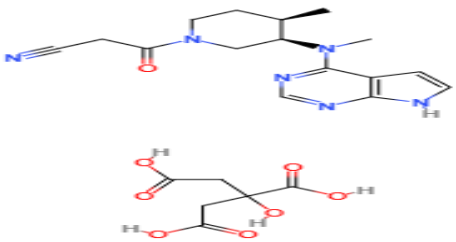
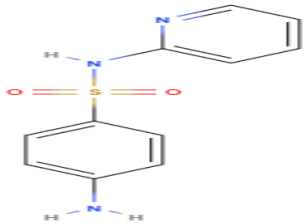
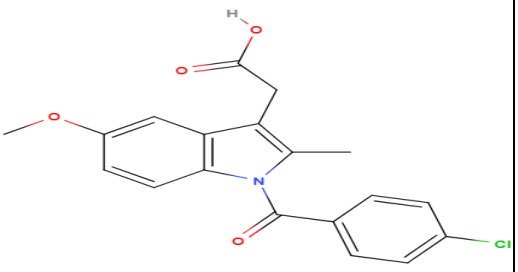
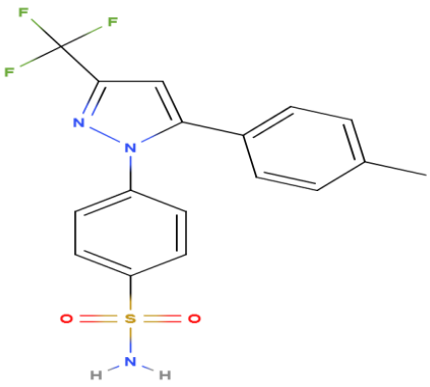
Table No 3: "Medications for Treating Rheumatoid Arthritis Based On Solid Lipid Nanoparticles"

Sr.No	Name of Medicines	Nanocarrier	Particle size (nm)/Zeta potential (mV)	Therapeutic effects	Structure	References
1.	Aceclofenac	Glycerol monostearate	189/ −32.51	arthritic effect and Anti-rheumatic		26
2.	Piperine	Glycerol monostearate	128.80/ −23.34	Anti-rheumatic arthritic effect		27
3.	Piroxicam	Glycerol monostearate	102/ 30.21	Anti-inflammatory effect		28
4.	Curcumin	Indian Gold	134/–	cascades of oxidative stress and immunomodulation.		29

2.2.3 Liposomes:

The first nanotechnology for drug delivery that has been effectively adapted for use in real-time therapeutic applications is liposomes. The idea of using a liposomal medication delivery technology has completely changed the field of medicine. Liposomes were first introduced by Alec Bangham in 1961. Since then, there has been ongoing study in the subject of liposomes, and they are now widely used for a variety of purposes, including the transport of drugs, biomolecules, and genes.[30]Several liposomal systems were delivered intravenously and accumulated in the bone marrow of Arthritis patients in an attempt to improve the disease's effectiveness. The colloidal, vesicular structures known as liposomes are made up of a few bilayers of lipids surrounding an equal number of fluid regions.[31]Liposomes are made from natural materials are harmless, recyclable, biocompatible, and immuneogenic. The bilayer is composed of phosphatidylcholine (PC), phosphatidylglycerol (PG), dipalmitoylphosphatidylcholine (DPPC), distearoylphosphatidylcholine (DSPC), cholesterol (CH), stearylamine, dicetylphosphate, or a mixture of these.[32]The dimensions, lamellarity, and effectiveness of encapsulation (EE), which is defined as the percentage of the drug that is effectively encapsulated in the liposomes, can all be affected by the creation process utilized to make the liposomes.[33]Multiple analytical approaches (UV-vis detection, High performance Liquid Chromatography, Gas Chromatography, GC-MS, etc.) can be employed to determine the concentration of incorporated chemicals, depending on the active component that is integrated in liposomes.There are direct and indirect ways of determining EEwhen the substance inserted is a protein.In contrast to direct approaches, which assess the entrapment Efficiency of the loaded protein in the nanoparticles, indirect methods consider the non-entrapped protein or medicine.[34]

Table No 4. "According To The Therapeutic Agent Used, Examples Of Liposomes Created For Rheumatoid Arthritis Treatment Are Listed Below. Each Liposomal Formulation's mean Diameter, Associated Molar Ratio, And Lipid Composition And Chemical Structure Were Listed"

Therapeutic Agent	Drug Delivery Nano Systems Developed	Lipid Composition (Molar Ratio)	Diameter (Nm)	Chemical Structure	References
Disease-modifying Antirheumatic Drug	Liposomes with incorporated methotrexate	DSPC:Chol:DSPE-PEG2000 (10:5:1) 100 [96,97] EL:Chol:PA (7:2:1)	100		35,36
	Tofacitinib citrate-containing liposomes	SPC:Chol (1:1)	55–63		37
	Liposomes with incorporated sulfapyridine	P-90G:Chol (6.3:3.1)	455–470		38
Nonsteroidal Anti-inflammatory Drug	Indomethacin-containing liposomes	SL:Chol:SA/DCP (7:3:1) EPC:Chol:SA/PG (1:0.5:0.1/0.2)	n.r 50or 100		39, 40
	Celecoxib-containing liposomes.	Lipova E120:Chol: DSPE-PEG2000 (9:1:0.25)	92		41

2.2.4 Niosomes:

Recently, interest in using vesicular structures like liposomes for drug delivery has increased. Liposomes have a number of drawbacks despite their versatility, including expensive formulation costs, instability at various pH levels, and a limited shelf life since lipids soon go rancid. To address these issues, scientists have developed a nonionic surfactant vesicular system known as a niosome by substituting non-ionic surfactants and cholesterol for the phospholipid content of liposomes. Niosomes have a higher level of chemical stability and a more inexpensive non-ionic surfactant than liposomes, which makes them more economical.They also increase drug delivery for the treatment of RA by penetrating the skin more deeply. Niosomes, when applied topically, extend the time that drugs stay in the stratum corneum and epidermal layer, increasing drug penetration into the skin, according to the study. Theoretically, they might reduce trans epidermal water loss and replenish lost horny layer lipids in the skin. This smoothes the horny layer, allowing drugs to enter more easily. Unlike vesicles that contain negatively charged, cationic, and amphoteric surfactants, niosomes lack charged surfactants and so do not produce bleeding or irritate cellular surfaces.[42]

The steroidal system (cholesterol), a crucial component of the cell membrane, improves the stiffness of the bilayer and has an impact on the fluidity and permeability of the bilayer.By shielding the drug molecules from unintended immunological and pharmacological consequences, this carrier system prevents the drug molecules from prematurely degrading and inactivating. Niosomes have recently been thoroughly explored for their ability to operate as a carrier for the transfer of drugs, antigens, hormones, and various other living substances. Drug insolubility, unsteadiness, and fast degradation have all been addressed using niosomes.[43]

Table No 5. "Distinctions between Liposomes and Niosomes"

Liposomes	Niosomes
More Costly	Low costly
Phospholipids can degrade due to oxidation.	Non-ionic surfactants, on the other hand, are stable in this environment.
No specific techniques are needed for such formulations in comparison to phospholipids for storage, handling, or purification.	In comparison, no specific processes are required for such formulations.
Phospholipids can be either charged or neutral.	Non-ionic surfactants are uncharged

2.2.5 Transferosomes :-

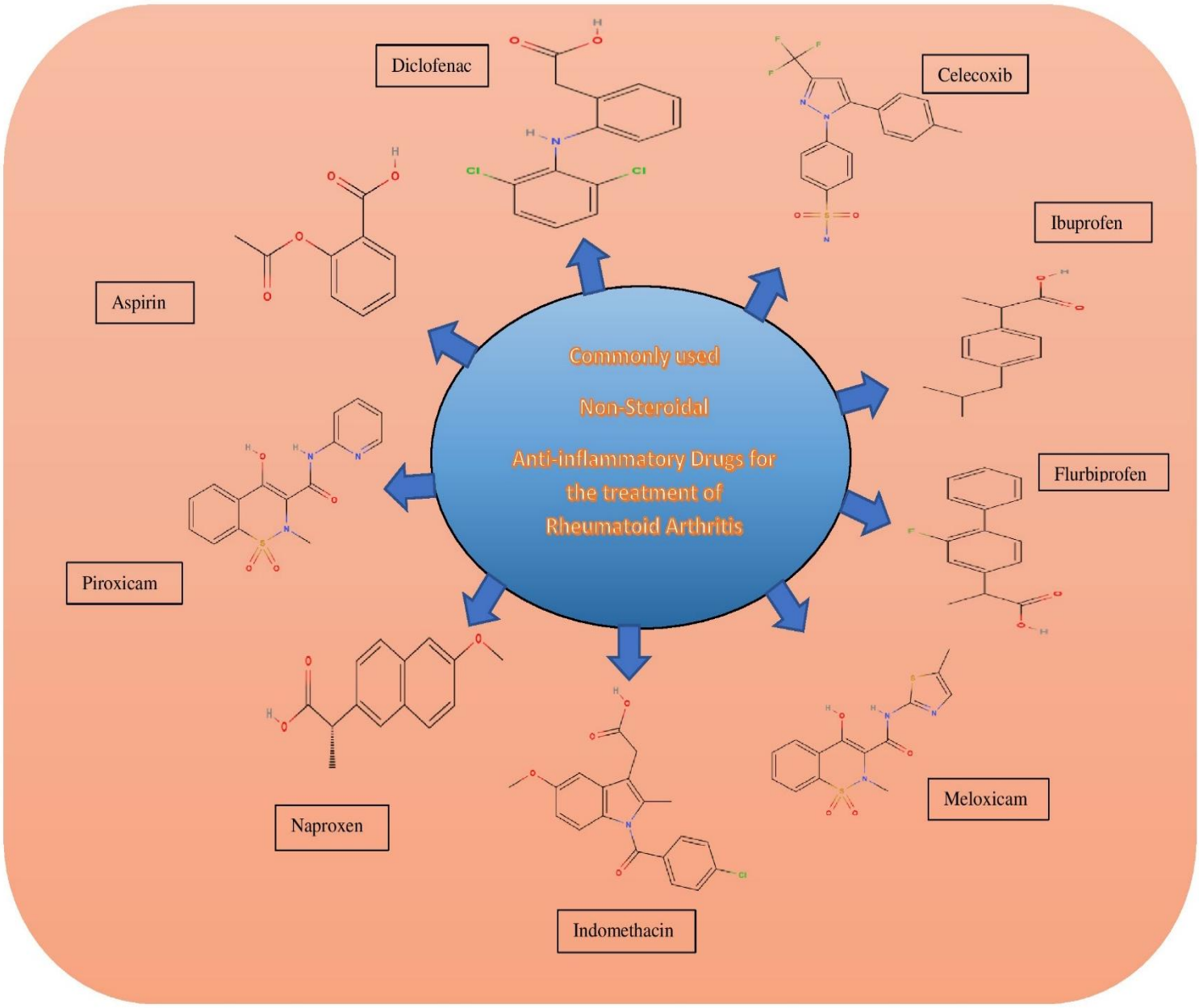
The transferosome is a newly developed vesicular nanoparticle for cutaneous medication delivery. The German company IDEA AG has registered it as a distinctive medication delivery method.Because they resemble liposomes so closely, transferosomes are sometimes known as ultra-deformable fatty acids, ultra-flexible liposomes, or stretchy liposomes. Physically, transferosomes and liposomes are the same since they both have at least one inner water compartment enclosed by a lipid bilayer. Transferosomes, on the other hand, include specialized surfactants known as border activators, which contribute to their elasticity. This is in addition to bilayer lipids.[42]Transferosomes provide many benefits, including a broad variety of solubilities, improved penetration, biocompatibility, and biodegradability. The transferosomes were created using the standard rotational evaporation and sonication process. It was developed with phospholipids, a surfactant, and a medication. Transferosomes are evaluated based on their vesicle size distribution, zeta potential, structure, and amount of vesicles per cubic mm.efficiency of entrapment, drugs inside it, Measurements of turbidity, degree of deformability, and permeability penetration power, Obstruction effect, the density of charges on the surface, Drug release in vitro, skin permeation experiments, physical steadiness. Transferosomes can be used for transdermal vaccination, targeted administration to peripheral subcutaneous regions, controlled release, and transfer of heavy substances.[44]

2.2.6 Ethosomes:-

Modern drug delivery methods like ethosomes largely work through the skin and only slightly penetrate biological membranes. Ethosomes are a drastically modified form of the widely used drug carrier liposome. Ethosomes are lipid vesicles that contain water, phospholipids, and alcohol (ethanol and isopropyl alcohol) in quite high concentrations. Ethosomes are phospholipid- and ethanol- and water-based soft vesicles. Ethosomes can range in size from thousands to millions of nanometers. Ethosomes have significantly greater transdermal flow than normal liposomes and reach the epidermal layers faster.Ethosomes are mostly employed in the transdermal delivery of medications.[(45)]There are many ways to make ethosomes, including the hot method, the cold method, and the traditional method of mechanical dispersion.[42] The Ethosomal technology is passive, discrete, and immediately commercially available.[45]

3.NANOMEDICINES USED FOR THE TREATMENT OF RHEUMATOID ARTHRITIS

Fig.5 Rheumatoid arthritis is frequently treated with non-steroidal anti-inflammatory medications (NSAIDs).



3.1Management of RA:

3.3.1 Non-steroidal anti-inflammatory drugs:

Due to their ability to reduce inflammation and relieve pain, nonsteroidal pain relievers (NSAIDs) are the most well-known and often used therapies for arthritic conditions.[46] These work by restricting the cyclooxygenase (COX) enzyme from converting arachidonic acid into prostaglandins.[47] NSAIDs are frequently used in the symptomatic therapy of other conditions in addition to their usage in rheumatoid arthritis (RA) and osteoarthritis (OA).Rheumatic disorders characterized by a variety of acute pain symptoms as well as chronic musculoskeletal discomfort.[48]However,The negative effects of this class of medications are causing growing concern. Some of the negative consequences include acute renal ischemia caused by prostaglandin inhibition-induced vasoconstriction, blood pressure changes, and increased bleeding due to platelet inhibition.[49] According to reports, non-selective NSAIDs are ulcerogenic and can lead to major upper gastrointestinal (GI) problems such perforation, blockage, and bleeding.[50] NSAIDs that are frequently prescribed to treat RA are represented in Fig.5.

3.3.2 Corticosteroids:

Corticosteroids, particularly glucocorticoids, are frequently used to treat inflammatory conditions such as respiratory conditions, rheumatism IBD (inflammatory bowel disorder), and other autoimmune diseases.[51]They reduce the synthesis of molecules that bind to cells, pro-inflammatory cytokines and chemokines, and other important mediators of inflammation by interacting with cytosolic glucocorticoid receptors.[52,53]In patients who are unresponsive to NSAIDs and DMARDs, glucocorticoids can be used at low doses to reduce these side effects, or patients can be given selective glucocorticoid receptor agonists instead.[54,55,56]

3.3.3 Disease-modifying antirheumatic drugs:

Medications used to treat inflammatory arthritis, such as RA, belong into the category of disease-modifying antirheumatic medications (DMARDs).Typical synthetic DMARDs, targeted synthetic DMARDs, and biological DMARDs are the three categories into which this class of immunosuppressive and immunomodulatory drugs can be subdivided.[57]These drugs have a sluggish onset of action and can require weeks or months to produce any pharmacological impact. DMARDs do not have a consistent mechanism of action, and the side effects of each medication differ.Methotrexate (MTX),

hydroxychloroquine, sulfasalazine, and leflunomide are examples of commonly used synthetic DMARDs.[58]

3.3.4 Biologics:

The most recent group of RA therapies are biological substances, also known asbiological response modifiers, and they have been in use for approximately ten years.These medications have been created to specifically target the inflammatory chemicals, cells, and processes that lead to tissue damage in RA patients. Several novel medications are currently in various stages of clinical testing and could be made available in the future.[59]The IL-1 receptor antagonist Anakinra, the anti-IL-6 receptor antibody Tocilizumab, the B cell depleting antiCD20 antibody Rituximab, the T cell signaling inhibitor Abatacept, the TNF-receptor fusion protein Etanercept, the anti-TNF PEGylated antigen-binding fragment Certolizumab Pegol, and the anti-TNF monoclonal antibodies are all used to treat arthritis.[60]

Table No .6 "The advantages and disadvantages of clinical drugs in RA treatment"

Classification	Drug	Advantages	Disadvantages
NSAIDs	Indomethacin Ibuprofen Diclofenac sodium	Rapidly reduce pain and inflammation by inhibiting COX	Inability to stop joint damage,gastrointestinal bleeding and kidney dysfunction
DMARDs	Methotrexate Sulfasalazine	Effective in controlling the disease progression	Take effect slowly and hepatic Sulfasalazine cirrhosis, kidney failure
GCs	Dexamethasone Prednisolone Betamethasone	Powerful inhibition of inflammation	Hypertension, osteoporosis Prednisolone and immunosuppression
Biological agents	Adalimumab Rituximab Anakinra	High specificity and efficacy	High cost, low responsiveness

CONCLUSION:

Innovative drug delivery techniques such liposomes, microspheres, nanoparticles, dendrimers, and transdermal delivery show great potential. It has been demonstrated that these medication delivery techniques are more effective than the traditional drug administration systems.It has been demonstrated that these medication delivery techniques are more effective than the traditional drug administration

systems. Although the current therapeutic choices, including NSAIDs, corticosteroids, DMARDs, and biologics, are very promising, they are also accompanied by quite a few drawbacks.

Nanotechnology, as one of the vital technologies of the twenty-first century, plays a major role in science in a variety of fields. Nano-drug controlled-release systems have gotten a lot of attention as a new drug delivery approach, particularly in the fields of targeted and localized drug administration, mucosal absorption drug delivery, and protein and polypeptide controlled release. Nanomaterials have unrivalled benefits. Applications for the treatment of rheumatoid arthritis using nanomaterials have shown potential. By using nanomaterials as drug carriers, standard anti-arthritis drugs' pharmacokinetics are changed, which improves the amount of medication deposited in joint tissues while reducing side effects. The efficiency of rheumatoid arthritis treatment has improved thanks to the use of nanomaterials with built-in anti-inflammatory properties, which are less harmful.

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