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NANOCARRIER POSSIBILITIES IN TREATMENT OF RHEUMATOID ARTHRITIS: A REVIEW

Bhumesh P. Lilhare*, Dr. Manjeet Singh, Dr. Rajesh Z. Mujariya, Lokesh I. Patle.

Student, Executive Director, Principal, HOD Pharmaceutics.
Department of Pharmaceutics,
Sardar Patel University, Balaghat

Abstract: Rheumatoid arthritis (RA) is a systemic autoimmune disease manifested by chronic joint inflammation which causes significant disability and death. RA affects women 3-5 times more than men, with a global frequency of roughly 0.3%-1%. Until now there no known cure for RA; the aim goal of treatment is to reduce symptoms. For the symptomatic relief of the disease therapy strategy entails constant drug delivery at maximum doses. Indomethacin, diclofenac, ibuprofen, celecoxib, and etorcoxib are examples of NSAIDs. These strong medications frequently have side effects. Desired effects, which significantly reduces patient compliance Furthermore, traditional nonsteroidal anti-inflammatory drugs. There are numerous formulation problems, such as limited solubility and permeability, as well as inadequate bioavailability. Gastrointestinal enzyme degradation, dietary interactions, and toxicity Researchers are working to overcome these obstacles. Have gone down the topical route of administration.

For the improvement of drug delivery in the RA therapy , a variety of adaptable Nano carriers with controlled physicochemical features, tailorable drug release patterns, or active targeting ability were created. Researchers now selected the topical drug delivery as a means of getting over these obstacles because it has better patient compliance and avoids the initial side effect of conventional oral administration. Furthermore, nanosized carriers like liposomes, nanoemulsions, niosomes, ethosomes, solid lipid nanoparticles, and transferosomes have been developed to improve the drug's ability to permeate through the skin's layers and reach the site of inflammation. These drug delivery methods have a high drug encapsulation efficiency, are non-toxic, and offer prolonged drug release.This review aims to provide an up-to-date progress regarding RA treatment using nanomedicines in the last 5 years and succinctly discuss the potential application of several newly emerged therapeutic strategies, such as fostering pro-resolving therapy, inducing antigen-specific tolerance, or managing immunometabolism for RA treatments.

Key Words: RA, Nano carrier, Nanomedicines.

I. INTRODUCTION:-

Rheumatoid Arthritis is a complex autoimmune disease that oftenly results in inflammatory infiltration, serious articular destruction, and extensive comorbidity in the cardiovascular system, gastrointestinal tract, and pulmonary tissues, and significantly decreases the life span of RA patients.
The WHO notes that RA is typically diagnosed between the ages of 20 and 40, during the productive years of adulthood, which lowers quality of life. A recent epidemiological investigation shows that women (4%) experience RA more frequently than males (2%), with a prevalence of 0.3–1%.
Over 50% of patients suffering from this disease eft full time work within just 10 years of disease development . Approximately 1.3 million Americans receive a RA diagnosis each year, or 41 out of every 100,000 persons.

From three months after the disease first manifests to two years later, when it has become more severe, the disease may be identified. A deeper understanding of the aetiology of RA has been made possible by the creation of newer cytokine treatments and improved diagnostic methods for antibody detection.

But the precise cause is still a mystery lymphocyte, macrophages, B cells, and dendritic cells are infiltrated along with the synovial inflammation that the patients are experiencing. If left untreated, the multiplication of synovial fibroblasts (SFs) and release of proteolytic enzymes may also result in irreparable deterioration of the bone and cartilage.

The main goal of current clinical therapies, such as non-steroidal anti-inflammatory drugs (NSAIDs), disease-modifying anti-rheumatic drugs (DMARDs), glucocorticoids (GCs), and biological agents, is to decrease the clinical manifestation of RA by dominating the immune system or by blocking specific inflammatory mediators7.

Ibuprofen and other NSAIDs can effectively reduce pain and oedema by blocking cyclooxygenase (COX). However, they are accompanied by significant gastrointestinal harm and are unable to alter the underlying illness process.

Nanomedicines, a hybrid of nanotechnology and medicine, use nanotechnology to passively or actively deliver pharmaceuticals to specific tissues, cells, or organs. Domains subcellular in passive targeting, aberrant vasculature and reduced lymphatic drainage in both solid tumours and inflammatory illnesses allow nano-sized materials to penetrate and accumulate within the neoplastic and inflammatory microenvironments.However, the extent of this purportedly increased permeability and retention impact is minimal. Actual efficacy may vary depending on both nanocarrier properties (such as size, shape, and surface charge) and factors related to tumour or inflammation biology (such as different types of tumours or inflammatory diseases, degree of vascularization and angiogenesis, and high interstitial fluid pressure). Active targeting, on the other hand, is the proper adjustment. When ligands are present on the surface of nanocarriers, an effective as well as precise interaction with specified cells we will discuss this in this editorial. Highlight active targeting strategies and applications Nanomedicines for the treatment of RA.

To date, the most extensively used approach for efficiently preventing opsonisation is nanocarriers treated with poly (ethylene glycol), i.e., PEGylation. Leaf Huang revealedthat the brush conformation, which may provide complete coating of nanocarrier surfaces, should be created by changing an optimal PEGylated nanocarrier with >8 mol% PEG. However, it is challenging to produce stable, PEGylated nanocarriers with a brush form while preserving the integrity of the lipid membrane. Furthermore, a high PEG density may inhibit the binding and absorption of nanocarriers by targeted cells, resulting in a paradoxical impact. Aside from to choose ligands that are specifically and effectively targeted at RA, disease pathophysiology must be paired with the PEG density, chain length, and structure, as well as covalent or physical adsorption coating processes. Angiogenesis and inflammation are the two key factors contributing to the advancement of RA. The salient characteristics There are several appropriate mediators. include chemokines, pro-inflammatory cytokines, growth factors, and other Proteases and cell adhesion molecules have been identified. involved in the process of angiogenesis development.

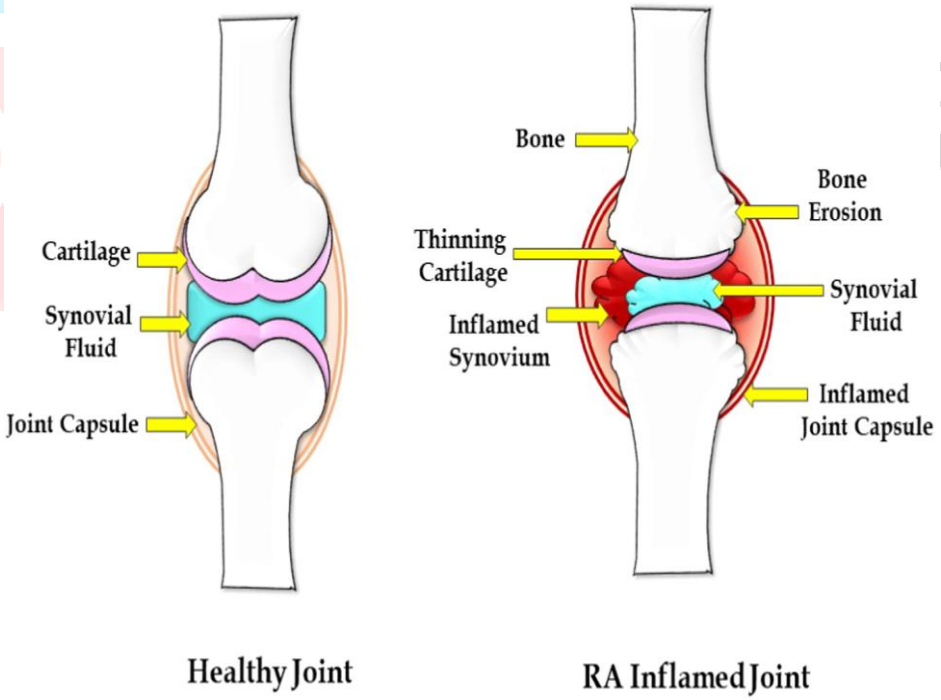

Fig1. Comparison between healthy joint and RA affected joint

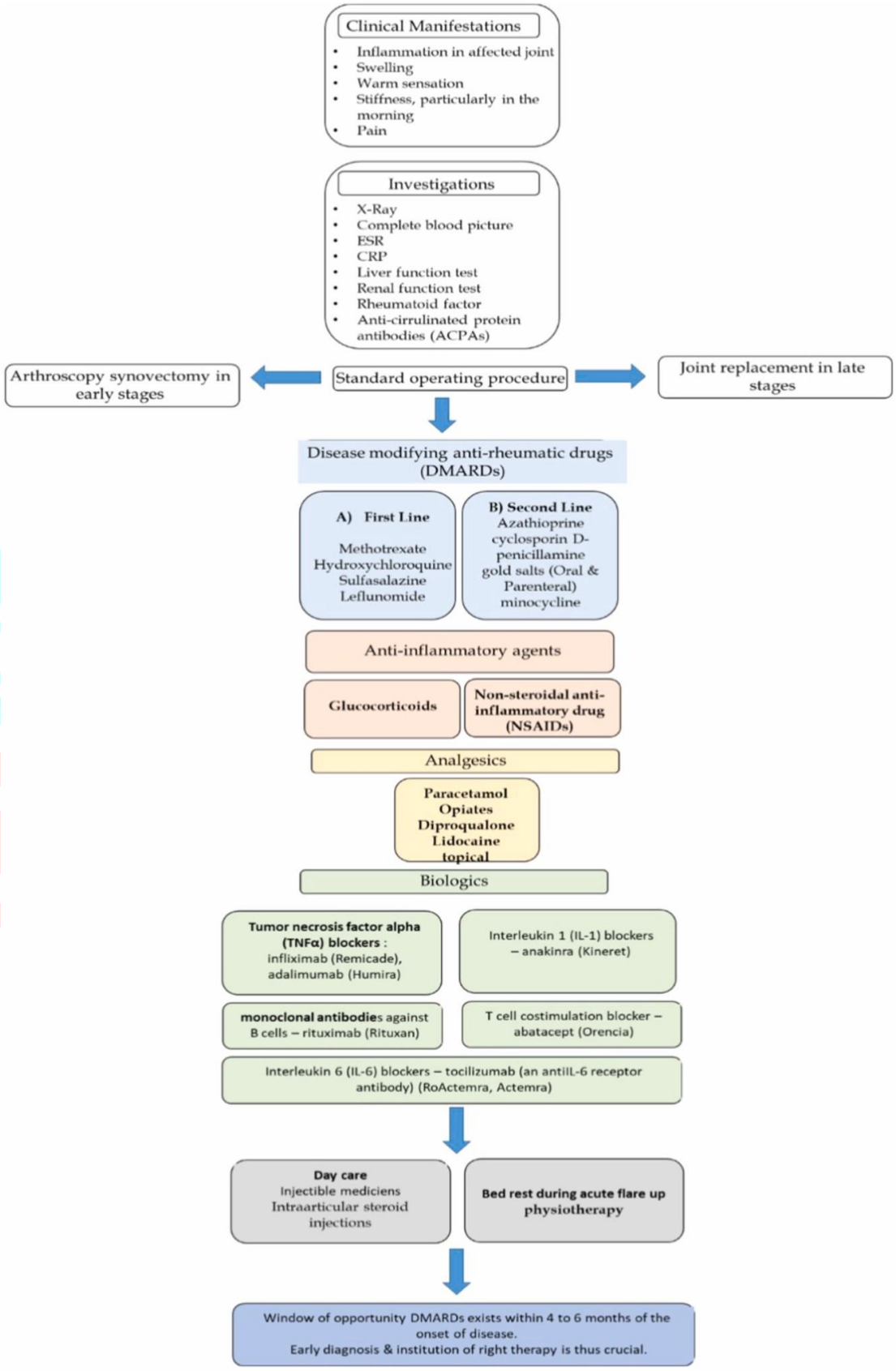

Fig2.Current treatment strategies in the treatment of RA

II. CURRENT TRATMENT STRATEGIES FOR THE RHEUMATOID ARTHRITIS:-

The usual RA treatment has changed over the past ten years as a result of developments in our knowledge of the RA pathogenesis. Non-steroidal anti-inflammatory drugs (NSAIDs) are still often used to relieve pain, but they are no longer considered first-line treatments because of their poor effectiveness, inability to stop the course of the disease, and harmful side effects.

Reduced joint pain and inflammation, improved joint function, and prevention of deformity and joint degeneration are the primary goals and strategies for managing rheumatoid arthritis. The Standard Treatment Guidelines for Rheumatoid Arthritis, published by the Ministry of Health and Family Welfare, Government of India, are shown in Fig. 2. Non-steroidal anti-inflammatory medications (NSAIDs), corticosteroids, and disease-modifying anti-rheumatic medicines are now being utilised to treat RA in India (DMARDs)Joint injury is prevented by biological DMARDs. In countries like the USA and Europe, similar therapeutic techniques are used. Guidelines for the optimum management of RA in the USA and Europe are periodically released by the American College of Rheumatology (ACR) and the European League against Rheumatism (EULAR). The ACR released updated guidelines for the use of DMARDs, biologic DMARDs, and glucocorticoids in high-risk populations, such as people with hepatitis, congestive heart failure, malignancies, and other serious conditions. Usage of vaccines in patients and the use of biologics in patients with concomitant tuberculosis (TB)beginning or receiving DMARDs or other medicationsMethotrexate (MTX) is advised as the first line of treatment by both ACR and EULAR. In addition, they advise adding biologic medications like TNFi for patients whose disease severity persists at a moderate or high level even after receiving treatment with DMARDs or for those who show insufficient responses to MTX [18]. Additionally, EULAR advises using MTX in conjunction with other DMARDs or glucocorticoids in certain therapeutic combinations. To obtain a weekly dose of around 0.3 mg per kg in such circumstances, the dose should be increased within 4-6 weeks. Leflunomide or sulfasalazine may be considered as a first-line therapeutic option if MTX contraindications or intolerance are noted.The design of such combination therapy is based on the patient's preferences, cost, and tolerance. Co-medication with inhibitors of the interleukin-6 pathway is also possible. Patients in durable remission need to taper biologic DMARDS or targeted synthetic DMARDs, particularly when these treatments are paired with a synthetic DMARD that is used more frequently. Biologic DMARDs that are abruptly stopped frequently cause flare-ups and may make the condition worse. The severity of the disease, the patient's tolerance, their financial situation, and any concomitant conditions should all be taken into consideration when doctors and patients decide on a course of therapy [20]. Table 1 lists the several dose forms used to treat RA and details each medication class's mode of action.

III. NEED FOR NOVEL NANOCARRIESRS IN RHEUMATOID ARTHRITIS:-

Maintaining a successful and regular active lifestyle depends on making an early diagnosis and recognising the development of RA. Non-steroidal anti-inflammatory medicines (NSAIDs) and glucocorticoids (GCs), which are primarily used to decrease pain, are a significant component of the traditional therapy approaches for RA. Indomethacin (IND), celecoxib (CLX), etoricoxib (EXB), meloxicam (MLX), and other commonly used NSAIDs work by blocking the inflammatory COX enzyme.Making an early diagnosis and recognising the onset of RA are necessary for maintaining a good and regular active lifestyle. Traditional therapeutic techniques for RA include non-steroidal anti-inflammatory drugs (NSAIDs) and glucocorticoids (GCs), which are largely used to reduce discomfort. The NSAIDs often used to treat inflammation, such as indomethacin (IND), celecoxib (CLX), etoricoxib (EXB), meloxicam (MLX), and others, act by inhibiting the COX enzyme.Leflunomide (LFU), methotrexate (MTX), sulfasalazine, clodronate, D-penicillin amine, and cyclosporinesome typical examples of DMARDs include tetracycline. Curcumin (CUR), capsaicin (CAP), and with annelids are a few well-known examples of herbal medicines that have been researched for reducing pain and inflammation brought on by RA. The majority of these medications are systemically injected and have unspecific side effects on extra-articular tissues and organs that are impacted by RA. Additionally, frequent dosing is necessary due to the short half-life and insufficient drug concentration at the site of action, which causes patient noncompliance. The need for the development of innovative drug delivery technologies, such as nanoemulsion, solid lipid nanoparticles, liposomes, ethosomes, noisome, and transferosomes, is developing in response to these restrictions.

Due to their lack of specificity, oral drug delivery methods can cause major side effects as gastric haemorrhage, renal dysfunction, and hepatic toxicity. Systemic adverse effects such bone loss, gastric ulcers, buffalo hump, etc. are seen with long-term usage of corticosteroids. The safety and patient compliance are significantly reduced by these off target consequence.

Transdermal medication delivery via the topical route, which is non-invasive and patient-compliant due to its simplicity of use, has received more attention in recent years. Along with these benefits, the dermal route of drug delivery also has the ability to bypass hepatic first pass metabolism and prevent drug inactivation by gastro-intestinal pH and enzymes. It also has a sustained action, dose flexibility, reduced side effects, and the ability to bypass hepatic first pass metabolism. However, a barrier to more widespread use of the transdermal medication delivery route is the stratum corneum's limited drug permeability.The stratum corneum is the top layer of the epidermis and is made up of lipid layers surrounding corneocytes, dead keratinized cells. As a result, the stratum corneum behaves like a strong, flexible barrier that is impermeable to water and restricts the diffusion of medicines. To improve medication penetration, researchers have experimented with a variety of approaches.

For improved penetration and to provide a longer residence time for an effective decrease of RA-induced inflammation, these formulations are typically added to a gel foundation.

As seen in Fig. 3, this review discusses cutting-edge drug delivery methods such vesicular systems and lipophilic nanoparticulate carriers. Nano emulsions and solid lipid nanoparticles are examples of lipophilic carriers. The vesicular systems, on the other hand, consist of noisome, ethosomes, and liposomes.

IV. VASICULAR SYSTEM:-

i) Liposome:-

Alec Bingham first introduced liposomes in 1965, and they have since been successfully used for therapeutic uses. Bilayer phospholipid vesicles with an aqueous centre are known as liposomes. These lipids are frequently employed as medicinal excipients and are typically non-toxic and biodegradable. These phospholipids also work as permeability enhancers to promote the percutaneous absorption of medications when delivered topically because their lipidic makeup is comparable to that of the skin.For sustained medication delivery via the skin, liposomes also function as a reservoir in the stratum corneum layer.Liposomal flexibility allows for the incorporation of both hydrophilic and hydrophobic medicines in the lipid bilayer and liposomal core, respectively .When a phospholipid layer is broken by an outside force, like sonication or stirring, or when it comes into contact with an aqueous phase, liposomes are created on their own. Film hydration, reverse phase evaporation, injection method, and freeze drying method are the procedures used in liposomal system preparation. Liposome skin permeability is influenced by lipid content, size, and surface charge. The drug encapsulation and drug release profile are both influenced by the liposome's lipid makeup. Begum et al. investigated thecholesterol's impact on the effectiveness of the liposomal encapsulation of the poorly water-soluble NSAID Celecoxib (CXB). According to their findings, liposomes with Outstanding CXB encapsulation efficiency was reported at the optimal concentration of cholesterol (12 mg), but as cholesterol levels increased, encapsulation and drug release decreased. Unilamellar vesicles (ULV), multilamellar vesicles (MLV), large unilamellar vesicles (LUV), and small unilamellar vesicles are the different types of liposomes (SUV)based on their size and lamellarity. However, because to their poor entrapment efficiency and stability issues, traditional unilamellar or multilammelar liposomes have few therapeutic applications.i.e., sudden drug release brought on by an unexpected membrane rupture. Multivesicular liposomes (MVL), which have numerous nonconcentric aqueous chambers encircled by a web of lipoidal membranes, were created by researchers to address these issues. These systems are different in size and composition from MLVs and ULVs. Compared to MVLs, which have a size range of 5-30 m, ULVs and MLVs have a size range of 1–5 m, providing more room for drug encapsulation. In addition, neutral lipids such triolein, tributyrin, and tributyrine are present in MVLs in addition to the usual liposome lipids, stabilising the membrane boundaries of the distinct multivesicularstructure. The numerous aqueous vesicular structures enable more hydrophilic medicines to be encapsulated. Jain et al., for instance, developed MVL filled withCXB- β-cyclodextrin complex.Studies on drug release revealed that CXB released slowly, or 72% during a 24-hour period, which was accounted for by the presence of different diffusion barriers. Even after 24 hours, a 40% reduction in paw volume was observed in a carrageenan-induced rat paw edema model, indicating that the gradual drug release sustained in-vivo anti-inflammatory efficacy. Greater paw edema reduction in vivo supported liposomal DEX's superiority to free DEX.

ii) Niosome:-

Vesicular structures like liposomes have drawn more interest recently for use in medication delivery. Despite their multifunctional capabilities, liposomes do have several disadvantages, such ashigh formulation costs, a lack of stability at different pH levels, and a short shelf life since lipids quickly go rancid. To solve these drawbacks, scientists have created a non-ionic surfactant vesicular system known as a niosome by replacing the phospholipid content of liposomes with non-ionic surfactants and cholesterol. Noisomes are more cost-effective than liposomes due to their affordable non-ionic surfactant and higher chemical stability. They also penetrate the skin more deeply, increasing drug delivery to treat RA.Noisome increase the residence period of medications in the stratum corneum and epidermal layer when given topically, according to studies, enhancing the drug's penetration into the skin. They may lessen Trans epidermal water loss and restore lost skin lipids from the horny layer, according to theory.This makes the horny layer smoother to make it easier for drugs to penetrate. In contrast to vesicles containing anionic, cationic, and amphoteric surfactants, noisome do not contain any charged surfactants, hence they do not cause haemolysis or irritate cellular surfaces. Some of the most popular non-ionic surfactants are alkyl ethers and alkyl glyceryl ethers, Surbiton fatty acid esters like span 60 and poloxethyelene fatty acid esters like tween 20, 40, and 60

Manosroi et al. used ethanolwhen diclofenac diethyl ammonium-containing noisome are created (DCFD). By lowering the stratum corneum lipids' melting point and consequently raising the lipid fluidity and skin permeability, ethanol effectively enhances penetration.Niosomes are also extremely elastic and can squeeze through dermal layer pores since ethanol is present in them. When compared to commercial gel (0.14 microg/(cm2 h)) with a comparable DCFD, the gel containing elastic niosomes showed significant fluxes of roughly 3.76 microg/(cm2 h) of DCFD., which supported these hypotheses in transdermal absorption investigations on rat skin.

iii) Transfersomes:-

Another emerging vesicular nanoparticle for drug administration via the cutaneous route is the transferosome. It is a unique medicine delivery system that the German business IDEA AG has registered. Because transferosomes closely resemble

liposomes, they are frequently referred to as ultra-deformable lipids, ultra-flexible liposomes, or elastic liposomes. Because both transferosomes and liposomes include at least one inner water compartment enclosed by a lipid bilayer, they are physically identical. But in addition to bilayer lipids, transferosomes also contain (10–25%) specialised surfactants called edge activators, which adds to its elastic nature. These edge activators, which are frequently single-chained or non-ionic surfactants, can weaken the lipid bilayer and reduce interfacial tension, enabling the vesicles to deform in response to mechanical stress from the environment with the least amount of energy.

In order to get better by controlling the flexibility of the vesicles during dermal penetration, the concentration of edge activators enables them to penetrate through the dermal barrier and along the transcutaneous gradient before reforming to their original diameter. There are two ways for transferosomes to enter the dermal layers:

This procedure results in the intracellular lipid pathway. Similar to conventional liposomes, transferosomes can encapsulate minute amounts of hydrophobic, hydrophilic, and very hydrophobic medications. In this way, transferosomes have been utilised to transport a wide range of pharmaceutical substances, such as anti-cancer drugs, corticosteroids, and nonsteroidal anti-inflammatory drugs (NSAIDs) used to treat RA

iii) Ethosomes:-

Although liposomes and niosomes offer superior drug encapsulation and solubility, their application is constrained since, due to their less flexible form, they are unable to penetrate deeply into the skin. Like niosomes and liposomes, ethosomes are lipidic vesicles, but differ in that they contain a larger proportion of ethanol (between 10 and 50 percent) .These vesicles' high ethanol content makes them elastic, which helps ethosomes efficiently pass through the skin's tiny channels and also increases the skin's lipids' fluidity These "soft vesicles" therefore serve as new vesicular transporters for improved cutaneous administration.Additionally, alcohol and the lipid vesicular system work together to promote drug entrapment. Ethosomes have been created using a variety of techniques, including the hot approach, the cold method, and the conventional technique for mechanical dispersion.
Tetradrine is a herbal medication that Fan et al. created as ethosomes and lipsomes for the treatment of RA symptoms. Tetrandrine-loaded ethosomes and liposomes were tested, and ethosomes were found to be significantly smaller (78 nm) than liposomes (99 nm). The system's net charge was thought to be altered by the high ethanol level, and it was also thought to provide some degree of steric stability, which reduced the size of ethosomes' individual vessels.In permeation studies using the franz vertical diffusion cell and rat skin, higher transdermal flux and 2.1-fold higher delivery of tetrandrine from ethosomes through the stratum corneum barrier than their liposomal equivalent were discovered. The greater anti-athritic action of ethosomes was further supported by in-vivo tests as considerableIn comparison to the liposomal treated group, the ethosome treated group showed signs of rat paw edoema.

As a result of lipid aggregation occurring in liposomes within a week of production, Sakdiset et al. discovered that ethosomes are more stable than liposomes in terms of stability. Typically discouraged in ethosomes are the electrostatic and bonding interactions between the phosphatidylcholine of SPC in liposomes, were suggested to be the cause of the aggregation.At the conclusion of 24 hours, Sarwar et al. reported that ethosomal CAP vesicles had superior permeation with a flow of 15 cm/h 10-3 in a modified diffusion cell, which was greater than that of both the hydroethanolic solution of CAP and the commercial CAP product Thermagel. The passage of capsaicin-loaded vesicles past the epidermal barrier was further validated by confocal laser scanning micrography. Thermagel only slightly lowered paw edoema by 15%, whereas CAP-loaded ethosomes dramatically inhibited paw edoema by 40% in CFA-induced arthritic rats.

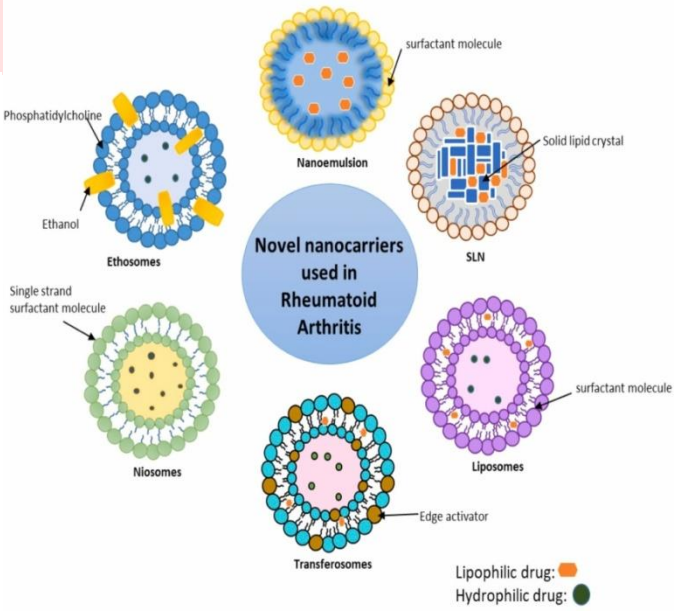

Fig3.Nanocarrier for the treatment of RA

V. LIPOPHILIC NANOCARRIER:-

i) Nanoemulsion:-

Nanoemulsions (NEs) are translucent, biphasic, isotropic, and kinetically stable colloidal dispersions containing vesicles smaller than 200 nm. These are often composed of water, emulsified oil, and amphiphilic molecules. NEs are used as drug delivery vectors for drugs like MLX, EXB, and CLX that are weakly soluble and permeable in order to increase their solubility and drug loading, hence increasing the drug's bioavailability. They are small enough to easily pass through the rough skin surface, which increases the medication's capacity to penetrate the skin.The first-pass metabolism following oral administration and the chemical/enzymatic degradation of the medications from the gut can both be prevented with this prospective strategy. Due to the small droplet size of NE, gravity forces dominate Brownian motion, favouring high kinetic stability toward coalescence, flocculation, and other processes. However, because to their thermodynamic instability, NEs require the addition of external energy in order to evolve. Either low energy emulsification or NEs can be produced.
(spontaneous emulsification and phase inversion technique) or high energy emulsification (high pressure homogenization, micro fluidization, and ultrasonication) Viscosity is an important property for stability and drug release. Cone and plate type rheometers are used for viscosity evaluation. Electrical conductivity is used to determine the outer phase. High conductivity concludes water as the outer phase and low conductivity concludes oil as the outer phase .EXB is a routinely used NSAID, which effectively reduces inflammation and alleviates pain by inhibition of COX, which in turn inhibit the synthesis of inflammatory mediators. However, oral administration of EXB results in serious gastrointestinal (GI) adverse effects upon chronic administration. To avoid unwanted side effects of NSAIDs such as gastrointestinal ulcers, bleeding and adverse cardiovascular events, Lala et al. encapsulated EXB in NE with a globules with a size of less 200 nm. In addition to having improved penetration through pig belly skin, EXB-NE significantly reduced rat carrageenan-induced paw oedema (84.61%) as compared to conventional gel (69.23%).

i) Solid lipid nanoparticle:-

Lipid nanoparticles such nanoemulsions, nanostructured lipid carriers, and lipid-drug conjugates have caught the attention of researchers in this area in recent years. In addition to this, solid lipid nanoparticles (SLNs), which have been produced in place of other conventional carriers, have the potential to increase cutaneous medication delivery of both hydrophilic and lipophilic medicines. The average diameter of SLNs, which are spherical colloidal structures, ranges from 40 to 1000 nm. Surfactants surround a lipid core with a high melting point to form SLNs. In some circumstances, hydrophilic polymers are also applied to SLNs to enhance their colloidal stability.Lipids utilised as solid lipid matrix include beeswax, stearic acid, cholesterol, glyceryl stearate (mono- and tri-), solid paraffin behenic acid, etc. The SLNs are prepared using additional components such surfactants, co-surfactants, preservatives, cry protectants, and charge modifiers. SLNs have a number of benefits, including great in-vivo tolerability, high physical stability, and little skin irritability, regulated drug release, and preservation of the integrated labile pharmaceuticals from degradation. By putting a targeting ligand on their surface, SLNs can also be employed to make poorly soluble medicines more bioavailable and to provide tailored therapy.SLNs display skin hydration and adhesiveness when applied topically. After application, a monolayer develops on the skin that has occlusive qualities and slows the skin's loss of moisture. As a result, the medication can penetrate deeper layers of skin because it lowers coenocyte packing and widens intercorneocyte gaps. High pressure homogenization (hot homogenization, cold homogenization), ultra sonication, solvent emulsification, micro emulsion based, double emulsion technique, and supercritical fluid based are the main methods for creating SLNs. According to studies, tiny particles exhibit greater evaporation barrier characteristics and increase occlusion. Lipid nanoparticle application volume, particle size, and lipid matrix crystallinity are all factors that affect this action.

The amount of lipid and surfactant present has a significant impact on how well the medicine is retained. Fluriprofen (FP) loaded SLNs were examined by Jain et.

for the impact of surfactant: lipid ratio on particle size and encapsulation effectiveness. Chosen as lipids were stearic acid and cholesterol, and Pluronic F-68 was chosen as the surfactant. The average particle size (70-807 nm) rose as the concentration of pluronic F-68 was raised from 0.4 to 1 of the total lipid content, and FLP entrapment decreased from 95% to 60% as a result. The FP-SLN topical gel also demonstrated continuous release for up to 5 hours.

Their composition exerts strong control over properties such as particle size, drug loading and release, and stability. The drug release profile is also impacted by the composition of the SLN lipid matrix, which also affects its physiochemical characteristics such particle size, surface charge, and drug entrapment efficiency [103]. For instance, after hot-melt homogenization, lipids with short-chain or complicated triglycerides, such as trimyristin, trilaurin, and Witepsol H35, generate a supercoiled melt that causes uncontrolled drug release [104]. Waxy materials and pure triglycerides, on the other hand, generate extremely crystalline structures with poor drug encapsulation [105,106]. Short chain triglycerides and waxes have been mixed by researchers to address these problems, resulting in a less ordered structure and appropriate drug encapsulation.

VI. LIMITATIONS FOR TREDITIONAL THERAPY AND ROLE OF NANOMEDICINES IN LAST DECADES:-

The main problems of traditional RA pharmaceutical dose were low patient adherence, a short half-life, poor bioavailability, and insufficient solubility, all of which may be addressed by exploring for innovative dosage options. Microparticles, nanoparticles, nano dispersions, nanocapsules, nanoemulsions, nanosuspensions, and other innovative RA therapy delivery techniques improve therapeutic efficacy by delivering the drug at a higher concentration to the target area. the utilisation of nanomedicine for RA therapy has increased significantly in the recent 10-15 years.In a preliminary study, indomethacin-loaded polymeric Micelles made of amphiphilic polyphosphate demonstrated encouraging findings implying that this sort of amphiphilic Copolymers can be used as injectable nano-carriers for a variety of applications. Actarit, a poorly soluble drug, was later discovered to be hydrophobic was encapsulated in solid lipid nanoparticles (SNLs) for intravenous administration, which reduces side effects such as gastrotoxicityas well as renal problems In mice, are intravenous therapy, actarit-loaded SLNs' total targeting efficiency (TEC)rose in the spleen from 6.31% to 16.29%, whereas theActarit's renal distribution was significantly reduced when compared to Polymeric nanocapsules were then added to the actarit solution. Were used to administer indomethacin, which demonstrated long-term treated rats with increased anti-inflammatory potential Inflammation models, as well as better gastrointestinal well-being.Because RGD is an inflammatory moiety, MTX-loaded poly(DL-lactic-co-glycolic acid) (PLGA)-Gold (Au) half-shell nanoparticles (MTX-PLGA-Au) and conjugated arginine-glycine-aspartic acid (RGD) peptides on the surface of the Au half-shell boosted MTX's potential as a RA treatment.

29 Several other nanomedicines have been reported as potential candidates for RA therapy, including MTX combined with nanoemulsions,30 siRNA-loaded chitosan nanoparticles,31 curcumin-loaded carboxy methyl cellulose acetate (CMCAB),32 exosomes as biomimetic particles,33 stimuli responsive liposomes,34 MTX and siRNA loaded carbon nanotubes,35 poly(amidoamine) dendrimers functionalized withchodrotin sulphate and with anti-TNF a to provide anti-inflammatory properties and mesoporous silica nanoparticles encapsulating dexamethasone to deliver traditional drugs

VII. CONCLUSION:-

Chronic usage of medications, including NSAIDs, corticosteroids, DMARDs, and biologics, is required for the treatment of rheumatoid arthritis and has been linked to peptic ulcers, osteoporosis, delayed wound healing, and gastrointestinal irritation. Malfunction of the liver and kidneys stifled the immunological response. Treatment must be site-specific in order to reduce side effects and increase therapeutic effectiveness. The development of nanocarriers that can efficiently penetrate the layer of skin when applied topically is the result of research into innovative topical delivery systems. The targeted inflamed joint will get medications via these nanocarriers in a targeted, localised manner. Additionally, they lessen the dosage of the drug administered, reducing the possibility of unintended side effects.

These delivery systems based on nanocarriers can also be used by patients who are members of high-risk populations. Vesicular systems and lipophilic nanocarriers have a lot of promise for targeted medication delivery to inflamed barriers. Lipophilic nanocarriers, such as solid lipid nanocarriers and nanoemulsions, increase the solubility of pharmaceuticals that are poorly water soluble, which enhances drug loading, confers stability, and aids in dose reduction. In terms of composition, surface modification, and drug encapsulation, liposomes are flexible. However, because the majority of it is made up of lipids, they are particularly susceptible to oxidative lipid breakdown. Niosomes are a good substitute for liposomes because they are made of surfactants, which are far more stable than lipids.Niosomes have excellent drug delivery characteristics like high drug loading efficiency, varied payload capabilities, and prolonged drug release, similar to liposomes. Monitoring the type of surfactants and their toxicological limits is essential, though. Similar in structure to liposomes, transfersomes have a unique edge coating of surfactants that renders them elastic and ultradeformable.

VIII. CONFLICT OF INTEREST:-

The authors declare that they don’t have any conflict of interes

IX. REFERENCES:-

1. Guo Q, Wang Y, Xu D, Nossent J, Pavlos NJ, Xu J. Rheumatoid arthritis: pathological mechanisms and modern pharmacologic therapies. Bone research. 2018 Apr 27;6(1):1-4.

2. Saxena A, Raychaudhuri SK, Raychaudhuri SP. Rheumatoid Arthritis: Disease Pathophysiology. InInflammation, Advancing Age and Nutrition 2014 Jan 1 (pp. 215-229). Academic Press.

3. mVenuturupalli S. Immune Mechanisms and Novel Targets in Rheumatoid Arthritis Rheumatoid arthritis Pathophysiology Biologics Novel targets.

4. Yap HY, Tee SZ, Wong MM, Chow SK, Peh SC, Teow SY. Pathogenic role of immune cells in rheumatoid arthritis: implications in clinical treatment and biomarker development. Cells. 2018 Oct 9;7(10):161.

5. Vickers NJ. Animal communication: when i'm calling you, will you answer too?. Current biology. 2017 Jul 24;27(14):R713- 5.

6. Kumar V, Kanwar JR, Verma AK. Rheumatoid arthritis: Basic pathophysiology and role of chitosan nanoparticles in therapy. InAdvances and Avenues in the Development of Novel Carriers for Bioactives and Biological Agents 2020 Jan 1 (pp. 481-507). Academic Press.

7. Alunno A, Carubbi F, Giacomelli R, Gerli R. Cytokines in the pathogenesis of rheumatoid arthritis: new players and therapeutic targets. BMC rheumatology. 2017 Dec;1(1):1-3.

8. Xiao S, Tang Y, Lv Z, Lin Y, Chen L. Nanomedicine–advantages for their use in rheumatoid arthritis theranostics. Journal of controlled release. 2019 Dec 28;316:302-16.

9. Burmester GR, Pope JE. Novel treatment strategies in rheumatoid arthritis. The Lancet. 2017 Jun 10;389(10086):2338-48..

10. Feng R, Yu F, Xu J, Hu X. Knowledge gaps in immune response and immunotherapy involving nanomaterials: Databases and artificial intelligence for material design. Biomaterials. 2021 Jan 1;266:120469.

11. Jain KK. Drug delivery systems-an overview. Drug delivery systems. 2008:1-50.

12. Singh AP, Biswas A, Shukla A, Maiti P. Targeted therapy in chronic diseases using nanomaterial-based drug delivery vehicles. Signal transduction and targeted therapy. 2019 Aug 30;4(1):1-21.

13. Perrie Y, Rades T. FASTtrack Pharmaceutics: Drug Delivery and Targeting. Pharmaceutical press; 2012.

14. Imming P, Sinning C, Meyer A. Drugs, their targets and the nature and number of drug targets. Nature reviews Drug discovery. 2006 Oct;5(10):821-34.

15. Weyand CM, Fujii H, Shao L, Goronzy JJ. Rejuvenating the immune system in rheumatoid arthritis. Nature reviews Rheumatology. 2009 Oct;5(10):583-8.

16. Wang Q, Sun X. Recent advances in nanomedicines for the treatment of rheumatoid arthritis. Biomaterials science. 2017;5(8):1407-20.

17. Yang M, Feng X, Ding J, Chang F, Chen X. Nanotherapeutics relieve rheumatoid arthritis. Journal of Controlled Release. 2017 Apr 28;252:108-24.

18. Baschant U, Lane NE, Tuckermann J. The multiple facets of glucocorticoid action in rheumatoid arthritis. Nature Reviews Rheumatology. 2012 Nov;8(11):645-55.

19. Wailoo A, Hernández Alava M, Scott IC, Ibrahim F, Scott DL. Cost-effectiveness of treatment strategies using combination disease-modifying anti-rheumatic drugs and glucocorticoids in early rheumatoid arthritis. Rheumatology. 2014 Oct 1;53(10):1773-7.

20. Timlin H, Bingham III CO. Efficacy and safety implications of molecular constructs of biological agents for rheumatoid arthritis. Expert opinion on biological therapy. 2014 Jul 1;14(7):893-904.

21. Sinha S, Ghosh B, Bandyopadhyay S, Fatima F, Bandi VK, Thakur P, Reddy B, Chary S, Talluri L,Gupta A, Kale AR.

Comparative evaluation of efficacy, pharmacodynamics, and safety of Hetero's adalimumab (Mabura®, Hetero Biopharma Ltd.) and reference adalimumab (Humira®, Abbvie Inc.) in patients with active rheumatoid arthritis on concomitant methotrexate therapy. BMC rheumatology. 2020 Dec;4(1):1-1.

22. Smolen JS, Aletaha D. Rheumatoid arthritis therapy reappraisal: strategies, opportunities and challenges. Nature Reviews Rheumatology. 2015 May;11(5):276-89.

23. C Recio M, Andujar I, L Rios J. Anti-inflammatory agents from plants: progress and potential. Current medicinal chemistry. 2012 May 1;19(14):2088-103.

24. Evans CH, Ghivizzani SC, Robbins PD. Arthritis gene therapy is becoming a reality. Nature Reviews Rheumatology. 2018 Jul;14(7):381-2.

25. Xiao S, Tang Y, Lv Z, Lin Y, Chen L. Nanomedicine–advantages for their use in rheumatoid arthritis theranostics. Journal of controlled release. 2019 Dec 28;316:302-16.

26. Wang S, Lv J, Meng S, Tang J, Nie L. Recent Advances in Nanotheranostics for Treat-to-Target of Rheumatoid Arthritis. Advanced healthcare materials. 2020 Mar;9(6):1901541