Current Pharmaceutical Letters and Reviews (CPLR)
Website: https://cplr.in/
ISSN: 3049-222X
Vol. 3, Issue 1, Jan-Mar, 2026
Page No.: 20-41

Review

Review Article on Nanocarriers in Management of Rheumatoid Arthritis

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DOI:
10.62896/cplr.3.1.02

Conflict of interest: *NIL*

Article History
Received: 12/01/2026
Accepted: 21/01/2026
Published: 13/02/2026

Abstract:
Rheumatoid Arthritis is a Chronic, complicated Inflammatory diseases mostly affect joints. It causes severe pain and persistent inflammation, and it can occasionally cause disability or even early death. Women are 3 to 5 times more likely than males, affecting between 0.3% and 1% of the world's population. Regretfully, there is currently no treatment for RA. Reducing symptoms and making it easier for people to go about their everyday lives is the main objective of therapy. To manage RA, High dosages of nonsteroidal anti-inflammatory drugs (NSAIDs) are frequently prescribed by doctors. like celecoxib, etorcoxib, diclofenac, ibuprofen, and indomethacin. Patients may need to take these medications regularly to find relief. On top of that, new strategies are being tested to improve treatment, especially when it comes to delivering medications in a way that's more comfortable and effective for patients. For example, researchers are exploring the use of topical treatments, which involve applying medication directly to the skin, avoiding some of the side effects that can come from taking pills.

Keywords: Arthritis, Transdermal Adhesions, Nanocarriers, Topical gel, DMARD, Inflammation

1. Introduction

One of the main concerns with RA is joint inflammation, the synovial membrane, which lines the joints. This inflammation can lead to serious issues like bone damage and the erosion of cartilage. When someone has RA, their joints often become swollen and painful, which can make everyday movements difficult. It's particularly frustrating because the disease commonly strikes individuals in their prime, typically between the ages of 20 and 40, hindering their quality of life **(Huang *et al;* 2022).** Statistics show that in well-off countries, about 4% of women develop RA, and many patients are unable to hold down full-time jobs just a decade after being diagnosed. In the U.S. alone, approximately 1.3 million people, or about 41 out of every 100,000, receive a new diagnosis of RA each year **(Huang *et al;* 2022).** Symptoms can start showing up as early as three months after the disease begins, or it might take up to two years for the condition to become fully established and more serious. **(Kumar *et al.,* 2016).** Understanding the mechanics of RA has come a long way, largely thanks to advancements in treatment and better ways to detect specific antibodies in the body, although the exact cause of the disease remains unclear **(Savithramma *et al.,* 2016)**. Research indicates B cells, T cells, dendritic cells, and macrophages ar e examples of immune cells. that invade the synovium, leading to inflammation. Over time, if untreated, cells can produce destructive enzymes and contribute to permanent damage in the bones and cartilage. Genetic factors, along with environmental triggers, are believed to play a role in who gets RA. For instance, a specific genetic marker known as the Human Leukocyte Antigen (HLA) has been associated with the disease **(Huang *et al;* 2022)**.

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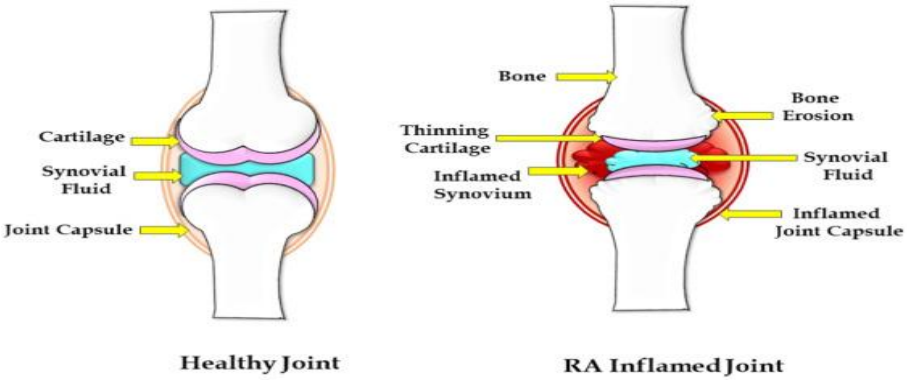
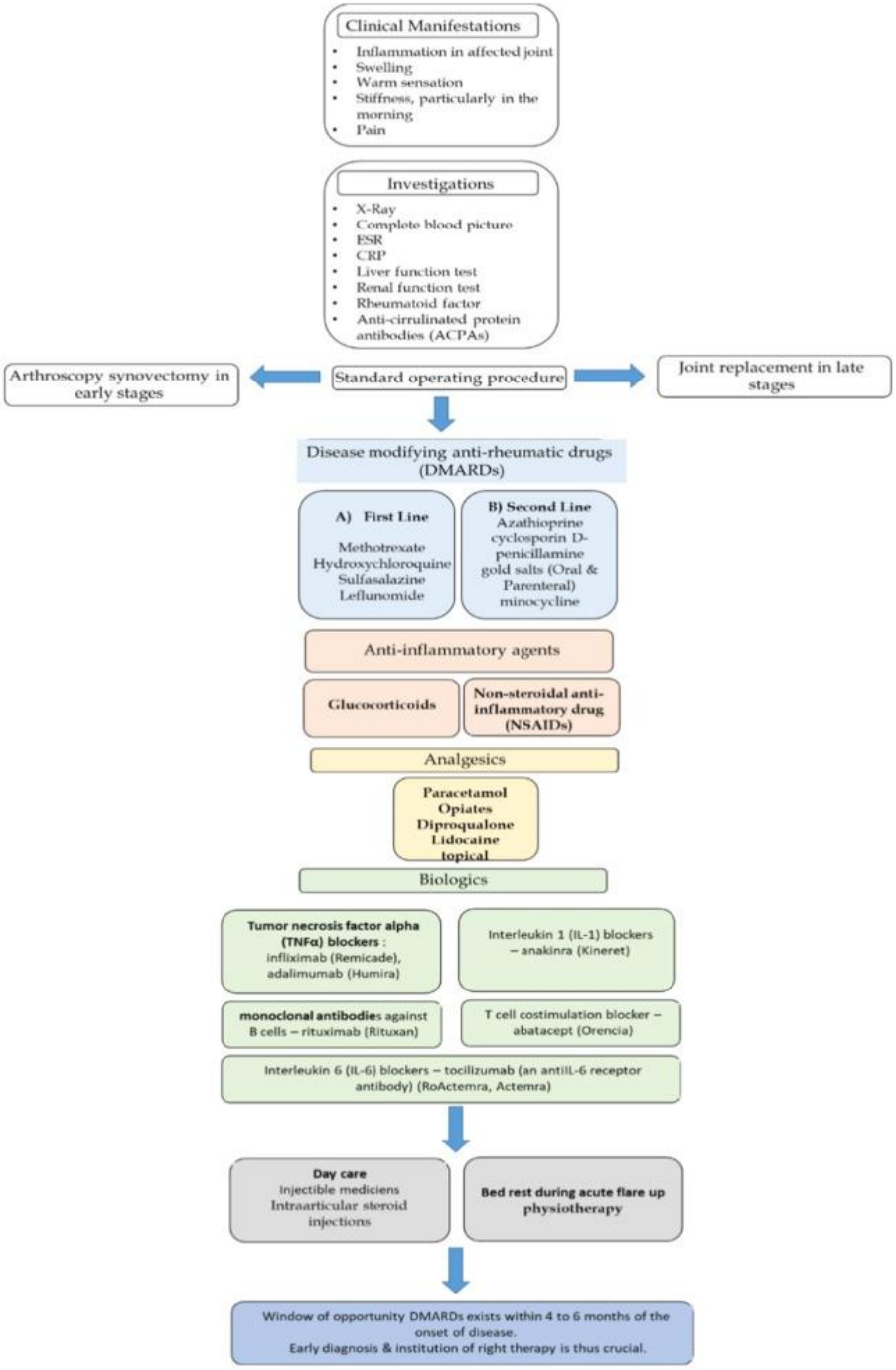


Difference Between Healthy and Inflammed Joint



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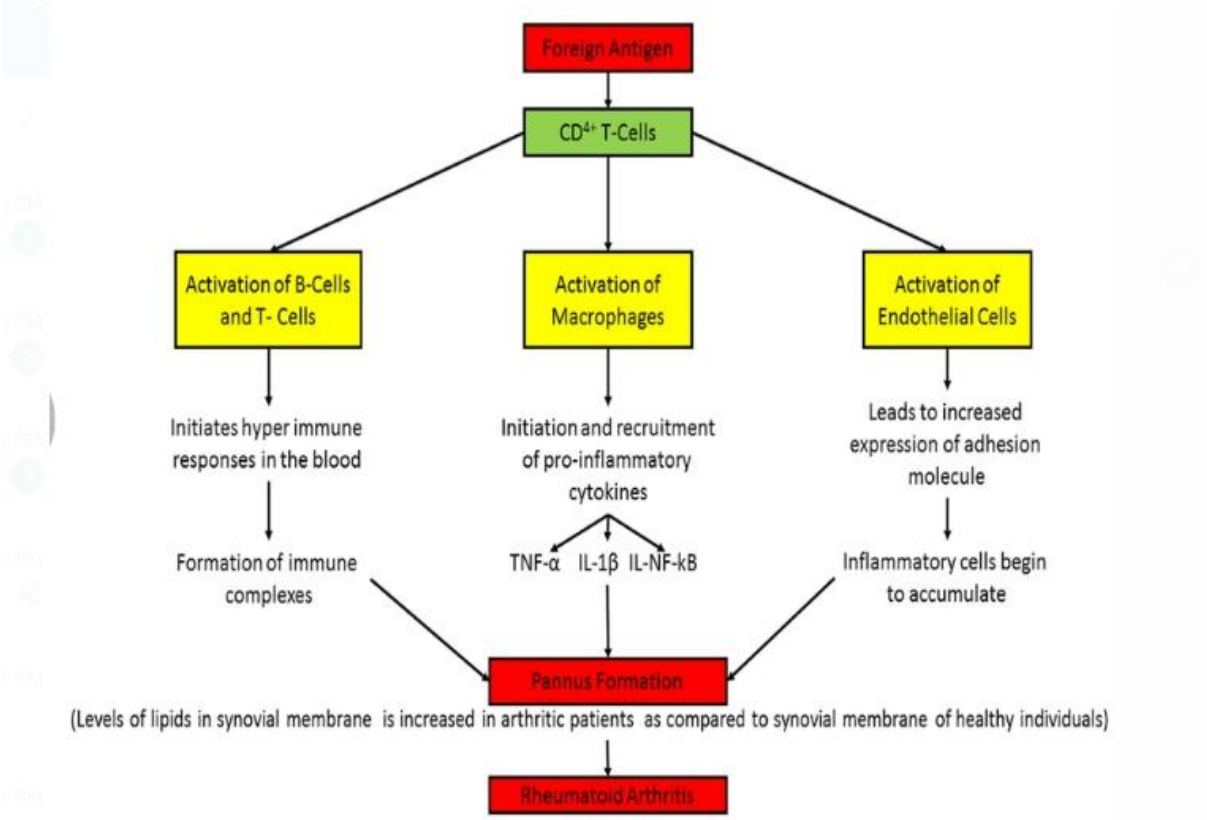
Cytokines, are small proteins released by cells, are crucial players in the inflammatory process of RA. Prostaglandin (PG), nitric oxide (NO), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF-α) are among the pro-inflammatory cytokines that are particularly produced and contribute to joint injury. Unfortunately, patients often have much higher levels of these harmful cytokines compared to anti-inflammatory ones, further amplifying the problem. One of the key destructive cytokines, interleukin-1 (IL-1), is produced in large quantities by immune cells in the synovium. IL-1 can provoke responses that affect B and T cells and encourage the production of compounds that break down cartilage. On top of that, TNF-α also contributes to bone loss and inhibits new bone growth. **(Dubey *et al.,* 2016)** As inflammation progresses, the lining of the joints thickens, leading to increased cartilage and bone destruction. Because the factors driving RA are so complex, targeting these pro-inflammatory cytokines and related pathways could provide new treatment avenues. Right now, there isn't a cure or preventive method for RA, so the emphasis remains on catching the disease early and starting treatment as soon as possible. This proactive approach is essential for maintaining a good quality of life and allowing those affected to live more normally and actively.

Pathophysiology of Rheumatoid Arthritis



2. Current Treatment Approaches of Rheumatoid Arthritis :

Reducing joint pain and inflammation, enhancing joint function, and halting more joint deterioration and deformity are the primary objectives of rheumatoid arthritis (RA) treatment. The primary focus of this evaluation is the Standard Treatment Guidelines for Rheumatoid Arthritis from the Ministry of Health and Family Welfare. Disease-modifying drugs Among the main pharmaceuticals used to treat RA in India are rheumatic medicines (DMARDs), Corticosteroids, biological DMARDs, and Non-steroidal Anti-Inflammatory Drugs (NSAIDs) (Dubey *et al.,* 2016). The efficacy of these therapies in delaying joint deterioration was demonstrated by Kany and associates in 2019. Similar methods are used to treat RA in other nations, such as the U.S. and Europe. In U.S and Europe,

groups such as the European League Against Rheu matism (EULAR) and the American College of Rh eumatology regularly update their guidelines for treating RA. For instance, in 2015, the ACR refined its recommendations regarding the use of glucocorticoids, biologic DMARDs, and DMARDs for patients at high risk for other serious conditions,

like hepatitis or cancer. Vaccinations are also important for patients starting or currently on DMARDs or biologics. Interestingly, both EULAR and ACR recommend methotrexate (MTX) as the first choice for RA treatment. If a patient's condition doesn't improve with MTX, they suggest incorporating biologic drugs like tumor necrosis factor inhibitors (TNFi). They also recommend combining MTX with glucocorticoids or other DMARDs to enhance treatment outcomes. Typically, if a patient needs a higher dose, this should be gradually increased within 4 to 6 weeks to around 0.3 mg per kg. If someone can't tolerate MTX or has contraindications, leflunomide or sulfasalazine can be considered as alternatives. A targeted synthetic DMARD or a biological DMARD may need to be added to a patient's treatment plan if they are unable to achieve clinical remission after taking at least two conventional DMARDs. Factors like patient preferences, costs, and tolerability play a key role in determining the best combination therapies.Moreover, interleukin6 pathway inhibitor s can be used in conjunction with traditional DMA RDs. but it's crucial that biologic or targeted synthetic DMARDs are reduced in patients who have achieved a stable remission, as emphasized by **Fan *et al.,* in 2020.**

Table 1: Lists of dosage forms for Rheumatoid arthritis treatments (Chando *et al.,* 2021)

S. No.	Form of Dosage	Class of Drug	Drug	Brand name
1.	**Tablets**	NSAIDS	Celecoxib	Celebrex
			Nabumetone	Relafen
			Indomethacin	Indicid
			Piroxicam	Feldane
		DMARDS	Leflunomide	Lefno
			Methotrexate	Imutrex
2.	**Capsules**	DMARDS	Sulfasalazine	Azulfidine
			Cyclosporine	Neoral
			Minocycline	Minoz OD
		NSAIDS	Indomethacin	Donica
3.	**Liquid Oral**	DMARDs	Azathioprine	Imuran
4.	**Injectable**	Biological DMARDs	Golimumab	Simponi
5.	**Topical**	NSAIDS	Diclofenac sodium	VOVERAN
6.	**Transdermal Adhesions**	NSAIDS	Diclofenac sodium	Voltarol, Nupatch

(Chando *et al.,* 2021)

3. Nanocarriers in Rheumatoid Arthritis

Now let's talk about the need for new ways to deliver medications for RA. The first step in treating RA usually focuses on pain control, which is why glucocorticosteroids and NSAIDs (**Guo *et al.,* 2018)** are often used. NSAIDs work by blocking the COX enzyme, which helps reduce inflammation (**Mahantey *et al.,* 2019).** However, taking NSAIDs for a long time can lead to severe adverse effects, such as hypertension and kidney damage , and heart issues, as well as gastrointestinal problems. It's important to address RA early on to maintain an active and fulfilling life. One important type of anti-inflammatory medications that aids in the management of RA pain and inflammation is glucocorticoids. **(Quan *et al.,* 2013)** Yet, using glucocorticoids over a long time can also cause side effects like muscle loss, diabetes, vision problems, bone loss, and hormonal issues. Second-line treatments called DMARDs help manage and decrease joint damage. To get around the limitations of current treatments, Researchers are creating new drug delivery vehicles, including ethosomes, liposomes, niosomes, transferosomes, solid lipid nanoparticles, and nanoemulsions. **(Pirmardvand *et al.,* 2018).** The goal is to create particles that can effectively target the inflamed areas of joints. This approach takes inspiration from cancer treatments, which use similar techniques to direct drugs to tumors due to the unique way those areas absorb medicine. When RA causes inflammation, the blood joint barrier can become significantly more permeable, which presents an opportunity for new drug delivery methods **(Shaji *et al.,* 2013).** An effective delivery system can help ensure medications target the painful areas without

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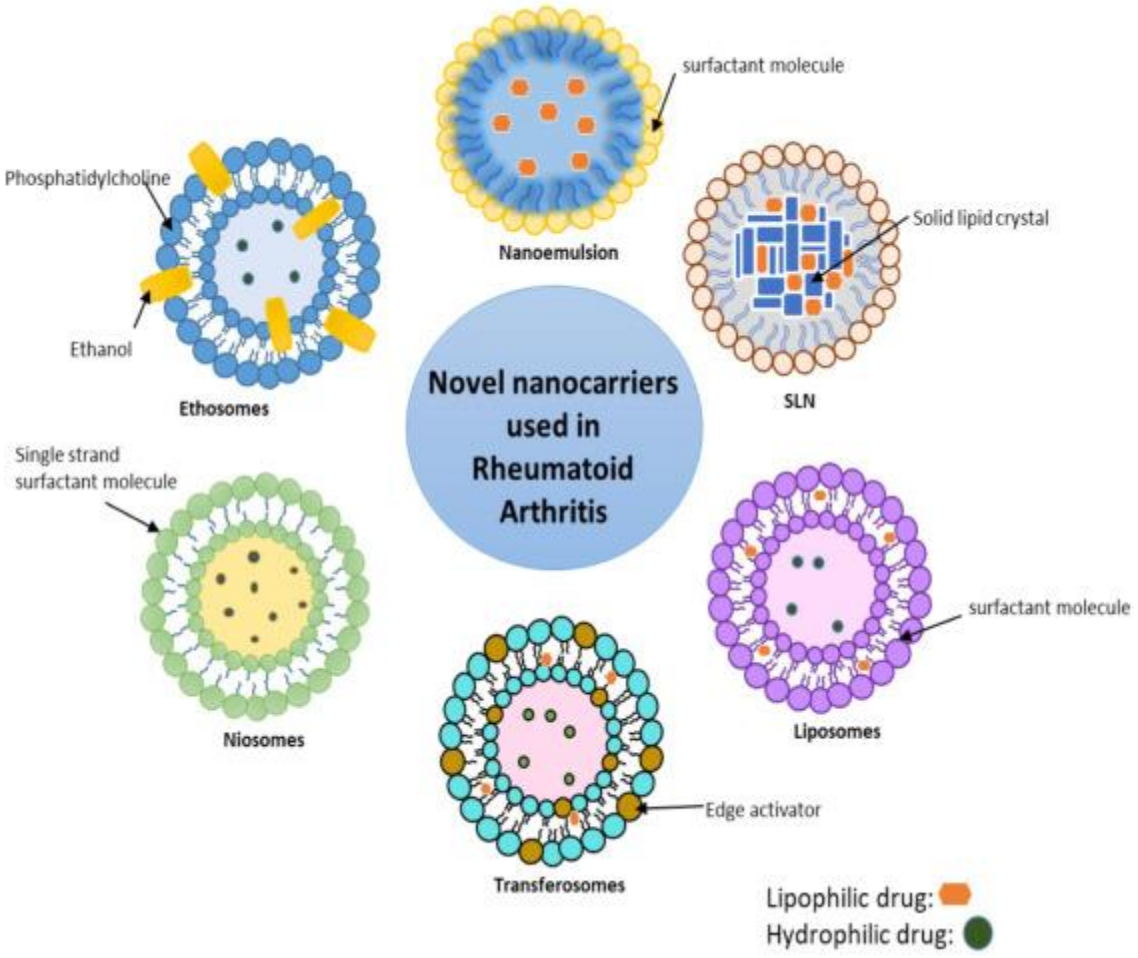
causing extensive side effects often seen with oral medications, which can affect the stomach and kidneys **(Higaki *et al.,* 2005).** Some research has focused on improving the delivery of medications through injections. For instance, injectable nanoparticles containing medications like betamethasone have been studied for steady release and targeted effects. While these methods have shown promise, there is still a challenge with how quickly the drugs clear from the body, necessitating frequent dosing.

Recently, there's been interest in transdermal delivery methods, which are less invasive and can improve patient compliance. These methods allow drugs to bypass the liver's metabolism and avoid some side effects that come from oral medications. However, one challenge is that many drugs do not easily penetrate the skin barrier effectively. To improve drug absorption through the skin, researchers are exploring various techniques like electroporation and microneedle technology. New drug formulations that incorporate nanoparticles have shown potential in overcoming barriers and offering longer-lasting treatment for RA. These formulations often enhance traditional gels to improve how well they work against inflammation **(Yuan *et al.,* 2005)** . In summary, development of new drug delivery systems, including various nanoparticle-based carriers, offers a promising avenue for improving RA treatment. By focusing on innovative ways to administer drugs, we hope to enhance their effectiveness and reduce the side effects that hinder patient participation and quality of life. The ongoing research in this area is crucial to advancing our understanding of how best to manage RA effectively.



4. Lipophilic Nanocarriers

I. Nanoemulsion (NE)

Nanoemulsions (NE) have emerged as a notable advancement in the field of colloidal dispersion formulation. These systems are characterized by their transparent appearance and qualities that are kinetically steady, biphasic, and is otropic, Typically, droplet diameters are smaller than 200 nm.Mostly made up of water, am phiphilic molecules, and emulsified oil, NE provide effective stabilization for emulsion systems. They have attracted significant interest as promising drug

delivery vehicles, especially for lipophilic compounds exhibiting low solubility and permeability, such as meloxicam (MLX), exicitinib (EXB), and celecoxib (CLX). The ability of NE to enhance the solubility and drug loading of these agents translates into improved bioavailability, facilitating their physiological absorption.

The small dimensions of Nanoemulsion allow for efficient penetration through biological barriers, particularly in transdermal applications, addressing the common challenges associated with gastrointestinal degradation and first-pass metabolism that frequently accompany conventional oral drug delivery methods. Due to the predominance of Brownian motion over gravitational force in nanosized droplets, It exhibit remarkable kinetic stability, effectively resisting issues such as flocculation, interface deformation, and coalescence. Nonetheless, it is critical to recognize that NE possess inherent thermodynamic instability, necessitating external energy input for their formulation. Both high-energy and low-energy emulsification techniques, such as phase inversion and spontaneous emulsification, can create these emulsions. Some of the most important factors in describing a nanoemulsion include electrical conductivity, viscosity, zeta potential, and particle size.. The particle size can be analyzed using freeze-fracture transmission electron microscopy, while the polydispersity index serves as an indicator of dispersion homogeneity. Viscosity, a substantial factor that influences both stability and drug release, is typically assessed using cone and plate rheometers. Additionally, measurements of electrical conductivity can help identify the outer phase of the emulsion; high conductivity values suggest water as the external phase, while lower values indicate an oil-based external phase.

Exicitinib , a widely recognized nonsteroidal anti-inflammatory drug (NSAID), is favoured for its capacity to reduce inflammation and alleviate pain by inhibiting cyclooxygenase enzymes, preventing the production of inflammatory mediators. However, there have been significant gastrointestinal (GI) adverse effects associated with the traditional oral administration particularly with chronic use. These adverse effects can include gastric ulcers and bleeding, as well as potential cardiovascular complications. To address the drawbacks associated with traditional NSAID delivery methods**, Lala *et al.,*** developed an innovative emulsion system encapsulating Exicitinib within nanosized emulsions. With globule sizes less than 200 nm, this formulation showed improved penetration through the skin of the pig's abdomen and a notable anti-inflammatory effect, as evidenced by an 84.61% inhibition of edema in a rat model of paw edema induced by carrageenan, which was higher than the 69.23% reduction that was attained with conventional gel formulations.

In a further investigation, **Shakeel *et al.,*** explored the encapsulation of Indomethacin (IND). Labrafil served as the oil phase, Transcutol-HP as a co-surfactant, Tween 80 as a surfactant, and water in a similar NE system. Their findings revealed that the IND-loaded NE offered superior and sustained anti-inflammatory effects compared to commercially available Indobene gel over a twelve-hour duration. However, they also noted an increase in the concentration of surfactants and co-surfactants raised concerns regarding potential skin irritation. This observation underscores the critical necessity for careful evaluation of safety, stability, and delivery efficiency in the formulation of NE.

The characteristics of nanoemulsions (NEs) are profoundly influenced by their composition, encompassing critical parameters such as droplet size, viscosity, and drug solubility. Research conducted by Lu et al. highlighted the pivotal role of NE size as a determinant of skin permeation. In a Franz diffusion cell model, their results showed that a D-limonene NE with a minimum size of droplet having 54 nanometers had the high penetration rates into rat abdomen skin. This contrasted sharply with NEs that possessed larger droplet sizes, ranging from 149 to 335 nanometers, which experienced significantly reduced permeation effectiveness. **El-Leithy *et al.*,** expanded upon these findings, elucidating the importance of formulation variables for enhancing drug solubility. They reported that manipulating the type and concentration of surfactants and cosurfactants within the NE formulation led to an impressive enhancement in the solubility of indomethacin (IND), achieving an increase by a factor of 610 compared to its solubility in water. Notably, their experiments indicated that NEs incorporating pluronic surfactants consistently yielded smaller globular sizes, ranging from 4 to 15 nanometers, as opposed to those formulated with Tween 80, which resulted in droplet sizes exceeding 100 nanometers. Due to their interaction with Indomethacin, which prevented pluronic molecules

from aggregating and hence decreased the size of the generated micelles, pluronic surfactants were found to selectively reduce droplet size..

In a complementary study, **Pathan *et al.,*** illustrated that an rise in the concentration of surfactants - specifically Polysorbate 80- facilitated a reduction in the droplet size aimed at the Meloxicam (MLX) topical administration inside NEs. Because of the surfactant's preferred location at the oil-water interface, this phenomenon has been connected to improved stabilization of oil droplets.

Furthermore, **Ilic *et al***. employed in addition to stabilizing NEs, sucrose esters facilitate the skin's absorption of the anti-inflammatory drug aceclofenac (ACF). Their *Ex vivo* skin permeation studies, utilizing porcine ear skin, established that the choice of surfactant significantly influenced NE permeation. The SE-stabilized NE exhibited superior penetration of ACF achieving the maximum steady-state permeation coefficient and flux in comparison to NEs stabilized with Polysorbate 80. This improvement in permeation performance was attributed to the stratum corneum's lipid matrix becomes unstable, which ultimately enhanced drug diffusion.

Moreover, the selection of gelling agents is critical in defining the physical properties of an emulgel. **Chandra *et al.*** investigated various gel types suitable for incorporating ginger extract within a NE framework. Their results indicated that Carbopol 934 yielded a remarkably transparent, clear, and homogeneous gel, devoid of grittiness, in contrast to the more turbid and cloudy gels produced using HPMC K4 and tragacanth, which were deemed unsuitable for emulgel formulation. Stability assessments of NEs can also be examined through percentage transmittance, a metric closely linked to particle size and distribution. An ideally monodisperse Water-in-oil (o/w) NE demonstrates transmittance that closely mirrors that of the aqueous phase, attributable to the even dispersion of droplets of oil. The oil type employed in the NE formulation significantly influences this transmittance parameter. **Nigam *et al.,*** for example, created two NE formulations loaded with capsaicin (CAP): one that used 10% oleic acid and the other that used Labrasol as the oil phase. Found that the Labrasol-containing NE exhibited an outstanding transmittance of 99%, while the formulation utilizing oleic acid was turbid and visually unclear. In their investigation into using NEs to improve curcumin's (CUR) penetration, a weakly water-soluble anti-inflammatory agent notorious for its limited skin permeability **Jeengar *et al.***, developed a formulation in which the oil phase, surfactant, and co-surfactant are Emu oil, Cremophor RH 40, and Labrafil M2125CS, respectively. For topical administration, the CUR-loaded NE was then included into a Carbopol gel. In comparison to CUR dispersions, ex vivo tests demonstrated that the NE dramatically enhanced CUR penetration in both aqueous and oily environments. *In vivo* investigations using a rat paw edema model caused by carrageenan further supported this improvement, where CUR-NE demonstrated a remarkable 66% inhibition of paw edema, in stark contrast to the 14.22% inhibition observed with pure CUR gel.

Similarly, Gokhale et al. enhanced a quercetin-loaded nano emulsion-based gel by combining oleic acid, arachis oil, Tween 20, and PEG-400 in a 15:6:6 ratio. These elements served as the co-surfactant, surfactant, permeation enhancer, and oil phase, in that order. Their studies of ex vivo penetration utilizing Wistar rat abdominal skin revealed that the QCT-NE gel facilitated a notable increase in permeation, recording 62% QCT delivery compared to only 35% from the free QCT gel at the 24-hour mark. Further in vivo studies supported these findings, indicating that the NE-loaded QCT gel led to a reduced paw circumference of 50 mm as opposed to the 71 mm observed in control subjects.

In another study, **Pleguezuelos-Villa *et al.*.** employed the biopolymer hyaluronic acid to stabilize NE formulations and enhance the bioavailability of the herbal anti-inflammatory drug mangiferin. When low molecular weight HA was added to NE formulations, their ex vivo penetration assays showed a striking 2.5-fold increase in mangiferin distribution. Additionally, in vivo assessments showed that, in comparison to control groups, those treated with mangiferin-loaded H hyaluronic acid, Inflammation was reduced by 20 times with nanoemulsion.

Finally, **Ghiasi *et al.,*** examined the efficacy of CAP - encapsulated NE in two distinct topical dosage formulations: Carbopol gel and a Cream. Their results demonstrated that in rat paw models caused by carrageenan, the CAP NE-gel was more effective at preventing edema. The enhanced effectiveness of the CAP NE-gel was hypothesized to result from the transformation of nanodroplets during the gelification process with Carbopol, which would

otherwise remain intact in the cream matrix. Carbopol gel's hydrophilic nature was inappropriate for preserving Capsaicin and NE's oily phase, both of which have hydrophobic properties. As a result, the cream formulation's therapeutic effects were reduced. Later, Hamed et al. created a diclofenac diethylamine gel based on NE concentrating on its therapeutic potential for treating rheumatoid arthritis, particularly in the context of the side effects associated with chronic oral administration of this medication.

The kinetics of release for the investigated nanoemulsions (NEs) demonstrated a controlled release profile spanning 12 hours, as characterized by the Korsmeyer-Peppas model, thus underscoring the promising role of NEs in topical therapeutic applications. Ibuprofen (IBF), one of the most commonly prescribed medications, faces significant challenges in effective administration through topical formulations, primarily due to its limited skin penetration capabilities. Research conducted by **Salim *et al.*** investigated the efficacy of IBF-loaded nanoemulsions made using the phase inversion composition method. They used different oil-to-surfactant ratios of 10:90, 20:80, and 30:70 with 80% water content, creating a ternary mixture, Cremophor EL, and palm kernel oil esters (PKOE). The resultant droplet sizes had a polydispersity index (PDI) of less than 0.2 and were regularly measured below 50 nm. It was found that the PDI and droplet size were significantly reduced when IBF was added to this nanoemulsion. This effect is mostly caused by the drug's amphiphilic properties and interactions with Cremophor EL. Importantly, the results of the IBF penetration flux through human skin from PKOE and Miglyol 812 nanoemulsions were comparable, suggesting that PKOE could be a good substitute for Miglyol 812 in the creation of NEs meant for topical medication delivery.

II. Solid Lipid Nanoparticles

Lipid-based nanoparticles—such as lipid-drug conjugates, nanoemulsions, and nanostructured lipid carriers have garnered attention regarding medication delivery systems in recent years. Among these innovative delivery modalities, solid lipid nanoparticles (SLNs) demonstrate remarkable promise in enhancing the cutaneous administration of both hydrophilic and lipophilic pharmaceutical agents when juxtaposed against conventional delivery methods. SLNs are defined as spherical colloidal systems, typically ranging between 40 to 1,000 nanometers in diameter. They consist lipid, often comprising elevated-melting-point, which are stabilized by surfactants. In some formulations, hydrophilic polymers may also be incorporated to further enhance colloidal stability.

The lipid matrix of SLNs can be made of a variety of substances, such as beeswax, stearic acid, cholesterol, mono- and tri-glyceryl stearate, solid paraffin, and behenic acid. Additionally, during the formulation of SLNs, a diverse array of other components including surfactants, co-surfactants, preservatives, cryoprotectants, and charge-modifying agents re utilized. SLNs possess numerous advantages; they exhibit high physical stability, provoke minimal skin irritation, provide controlled drug release, and offer protective properties for labile drugs, thereby preventing degradation. Importantly, By carefully placing particular ligands on their surfaces, It has been demonstrated that SLNs increase the bioavailability of poorly soluble substances and allow for customized treatment. When applied topically, SLNs not only improve skin hydration but also increase adhesion to the skin's surface. Upon application, they form an occlusive monolayer that aids in moisture retention by effectively minimizing transepidermal water loss. By reducing corneocyte packing and causing intercorneocyte gaps to open, this occlusive action makes it easier for medicinal medicines to enter deeper layers of the skin. The primary methods for producing SLNs are double emulsion, solvent emulsification, and microemulsion-based techniques.

methodology, ultrasonication, high-pressure homogenization (both hot and cold), and supercritical fluid production procedures.

Research indicates that smaller particle sizes exhibit enhanced barrier properties against evaporation, thereby leading to increased occlusive efficacy. The volume of the applied formulation, the size of the particles, and the lipid matrix's crystallinity are some of the variables that affect this increase. Furthermore, the quantities of surfactants and lipid components are crucial in determining the effectiveness of drug entrapmentIn a notable study, **Jain *et a.,*.** examined the influence of the surfactant-to-lipid ratio on the particle size and encapsulation efficiency of solid lipid nanoparticles loaded with flurbiprofen (FP). Pluronic F-68 served as the surfactant in this investigation, while stearic acid

and cholesterol were employed as lipid components. The investigation's findings demonstrated a favorable correlation: when the concentration of Pluronic F-68 was raised from 0.4 to 1.0 of the total lipid content, the average particle size grew from 70 to 807 nanometers, but the efficacy of FP encapsulation reduced from 90% to 60%. Crucially, the FP-loaded SLN topical gel showed continuous release for up to five hours, indicating the potential therapeutic application of the improved delivery methods. The unique compositions of solid lipid nanoparticles play a crucial role in determining their stability, release characteristics, drug loading capacity, and particle size. The lipid matrix has a major impact on the release dynamics of encapsulated pharmaceuticals in addition to dictating basic physicochemical characteristics such particle size, surface charge, and drug entrapment effectiveness. For example, lipids with complicated triglycerides or shorter chains, such as Witepsol H35, trimyristin, and trilaurin, when subjected to hot-melt homogenization, yield a supercooled melt that can lead to uncontrolled drug release. In contrast, the application of waxes and purely triglyceride compositions tends to result in highly crystalline structures, often associated with suboptimal drug encapsulation.

In order to overcome these obstacles, research has focused on the novel fusion of waxes and short-chain triglycerides, which results in a less structured matrix structure that enables sufficient drug encapsulation. A study by **Chantaburanan *et al.*** investigated the effects of a binary solid lipid matrix including cetyl palmitate and the triglyceride Softisan 378 on lipid crystallinity and drug release behavior in SLNs loaded with ibuprofen (IBF). The findings demonstrated that when triglyceride S378 levels rose, the particle size decreased as well, which was explained by a decrease in the dispersed phase's viscosity. Interestingly, IBF's encapsulation efficiency within the SLNs ranged from 98.86% to 99.98%, demonstrating nearly full drug entrapment. Following an analysis of drug release dynamics in a phosphate buffer at pH 5.5, the findings revealed a biphasic release profile consisting of an initial rapid release phase followed by a persistent release phase. The accumulation of IBF at the SLNs' outer shell or interface was thought to be the cause of the initial fast release. Interestingly, the release rate of IBF reduced as the concentration of triglyceride S378 increased. This phenomenon is thought to be related to the drug's localization within the liquid S378 nanocompartments scattered throughout the solid lipid matrix.

Furthermore, using excipients made of lipid mixtures has been a part of other tactics. Lipids including Geleol, Compritol 888 ATO, tripamitin, and Precirol ATO 5 are frequently included in SLN formulations. These mixtures of mono, di, and triglycerides create crystalline structures that are less than ideal and have many flaws, which allows for sufficient drug loading. A noteworthy study by **Verma *et al***. showed how to make pirfenidone-loaded SLNs (PIR-SLNs) with polyvinyl alcohol as the surfactant and tripamitin as the lipidA remarkable 85% drug entrapment effectiveness and a particle size of 435 nanometers were obtained from the improved formulation. Additionally, our analysis showed that the highest particle size in Compritol SLNs was around 1,000 nanometers, followed by Precirol at around 980 nanometers and Geleol at about 700 nanometers. Particle size increased noticeably when the lipid content increased from 5% to 10%; this was attributed to the increased aggregation of lipids at higher concentrations.

On the other hand, **Syed *et al.*** results showed that mean particle size and lipid concentration more especially, glyceryl monostearate (GMS) in SLNs loaded with azathioprine (AZA) were inversely correlated. This surprising result was ascribed to GMS's co-surfactant characteristics, which desrease the surface tension and enhance the development of small SLNs.

Interest in the creation of solid lipid nanoparticles (SLNs) for medication administration has significantly increased in recent years: vehicles, primarily because of their potential to increase therapeutic agent bioavailability and entrapment efficiency. Higher concentrations of mono, di, and triglycerides all of which are strong solubilizing agents have been shown in recent studies for the improved entrapment effectiveness for azelaic acid (AZA). Moreover, it has been shown that the creation of SLNs is strongly influenced by the preparation medium's viscosity. The medium becomes more viscous as the lipid concentration rises, which speeds up the nanoparticles' solidification. Drug encapsulation is improved by this accelerated solidification process, which limits drug diffusion from the exterior phase during nanoparticle formation.

Urbán-Morlán *et al.,* conducted a comparative investigation to evaluate the colloidal stability of cyclosporine-loaded Solid Lipid Nanoparticles prepared using Compritol 888 ATO and Gelucire 44/14.

A crucial parameter for assessing these colloidal dispersions storage stability was the zeta potential measurements. It should come as no surprise that the SLNs made using Compritol had a low zeta potential of less than 30 mV, which caused them to destabilize quickly in contrast to their Gelucire counterparts, which showed better dispersion stability. When it came to the stability of the cyclosporine content, it was found that the drug concentration significantly dropped after three months of storage; this drop was ascribed to the drug's leaching from the lipid matrix. A polymorphic alteration of the lipid was shown to be the fundamental cause of this event, which ultimately reduced the amount of space available within the matrix and facilitated drug release.

To determine the therapeutic efficacy of drug - loaded SLN, evaluation under *In vivo* settings is required. In this regard, **Bhalekar *et al.*** conducted a study with SLNs loaded with piperine (PIP) and achieved a remarkable entrapment efficiency of 78.71%. Their in vivo results showed that the untreated arthritic control group experienced severe bone and joint degradation. On the other hand, rats treated with these SLNs for adjuvant-induced arthritis showed notable decreases in paw volume. Interestingly, paw volume decreased more with the topical formulation of piperine in SLN gel than with the oral SLN formulation. The primary cause of this discrepancy in effectiveness is the drug's diverse biodistribution; a locally applied agent achieves a larger concentration at the application site, while oral preparations necessitate systemic circulation. Additionally, ex vivo studies on rat skin showed that PIP was significantly localized within the skin, making up 79.33% of the total, with only 4.53% remaining on the skin's surface.

In another study, **Bhalekar et al.** evaluated the efficiency of gel-based chloroquine SLNs against a rat model of adjuvant-induced arthritis. When compared to a commercially available chloroquine phosphate gel, the radiographic and histological evaluations showed less damage to the bone and cartilage. **Mohammadi-Samani *et al.*** comparison study, which examined the skin penetration of piroxicam from SLNs in contrast to a conventional piroxicam gel formulation, complemented this body of research. Their results unequivocally showed that the SLN gel greatly improved the drug's penetration, underscoring its promise as an excellent delivery method for the management of rheumatoid arthritis (RA)..

Researchers have started looking into using nanocarriers for dual agent therapeutic delivery in addition to these discoveries. This novel method minimizes any adverse effects by allowing for lower concentrations of each treatment while simultaneously increasing the therapeutic effects of the drugs. In a noteworthy study, **Vijaya *et al.***, created SLN for the simultaneous administration of doxycycline and methotrexate using Pluronic F-68 as a surfactant and lipid tristearin as the matrix. With zeta potential of -9.6 mV and a particle size of 157 nm, their studies showed entrapment efficiencies of 79% for doxycycline and 65% for methotrexate. Furthermore, both compounds exhibited a sustained release profile over a two-day period, according to in vitro drug release tests. These results highlight SLNs' promise as both single-drug delivery vehicles and effective substitutes for combination therapy, especially for treating chronic inflammatory diseases like RA. Furthermore, The therapeutic efficacy of herbal extracts in the treatment of RA has been hotly debated in the literature. However, their inherent poor solubility in conventional formulations usually restricts their wider application. SLNs were created by **Jeevana *et al.***, to increase the solubility of curcumin (CUR), a plant with anti-inflammatory properties. in order to address this problem. Concentrations ranging from 98.7% to 99.3% were obtained by integrating CUR into SLNs, suggesting little loss during formation. Goat skin ex vivo tests showed that the SLN topical gel had an impressive cumulative drug release of 76.93% within the first half hour of application. corresponding Rats treated with CUR-loaded SLNs showed no paw deformities and a noticeable decrease in paw swelling, but untreated rats showed visible paw deformities by X-ray radiography analysis, according to in vivo pharmacological studies. The idea that SLNs offer a viable approach to enhancing medication distribution and therapeutic results in the treatment of rheumatoid arthritis is supported by this strong data.

5. Vesicular systems

I. Liposomes

The concept of liposomes, initially introduced by Alec Bangham in 1965, has undergone substantial

development, leading to a diverse array of therapeutic applications. Liposomes can be defined as bilayer phospholipid vesicles that encapsulate an aqueous core. The phospholipids not only serve as structural elements but also function as non-toxic and biodegradable pharmaceutical excipients compatible with biological systems. A significant characteristic of liposomes is their ability to enhance permeability, especially in the context of transdermal drug delivery. This enhancement can be largely attributed to the lipid composition of liposomes, which closely mimics the lipid bilayer of human skin, thereby facilitating the percutaneous absorption of pharmacological agents. The "Donnan exclusion effect" is a common term used to characterize the process behind this enhanced permeability, especially when it comes to cationic lipids.

Liposomes efficiently serve as reservoirs in the stratum corneum, facilitating the long-term passage of medications through the skin. A noteworthy study by Puglia et al. demonstrated the efficacy of indomethacin (IND)-loaded liposomes combined into a gel matrix for topical delivery. Their findings indicated that the hydrogel containing IND-liposomes resulted in a significantly prolonged anti-inflammatory effect in healthy human volunteers experiencing induced erythema compared to a formulation featuring free IND. Specifically The steady release of IND seen over a six-hour period was linked to the formation of an IND reservoir in the stratum corneum.

In a similar vein, research by Tatheer et al. further investigated the performance of prednisolone (PD) encapsulated in a liposomal gel against free PD in hydrogel formulation. Their results revealed that the liposomal gel exhibited superior drug entrapment and an extended drug release profile.

The versatility of liposomes allows for the encapsulation of hydrophilic and hydrophobic drugs within their lipid bilayer and core, respectively. is one of their main advantages. When the phospholipid layer is disturbed by outside factors like Ultrasonication,, liposomes usually form on their own. Liposomal systems have been prepared using a variety of approaches, including as freeze-drying procedures, film hydration, reverse phase evaporation, and injection techniques. Crucially, factors including size, surface charge, and lipid content have a big impact on how well liposomes penetrate the skin. Drug release characteristics and encapsulation effectiveness are both impacted by the lipid composition. Begum et al.'s study clarified how cholesterol improves the encapsulation effectiveness of celecoxib (CXB), a non-steroidal anti-inflammatory medicine (NSAID) that is poorly soluble in water. According to their research, liposomes with an ideal cholesterol content of 12 mg showed exceptional encapsulation efficiency for CXB; however, encapsulation efficiency and drug release decreased beyond this ideal level.

Based on structural characteristics including size and lamellarity, liposomes can be categorized as giant unilamellar vesicles (ULV), multilamellar vesicles (MLV), or unilamellar vesicles (ULV). LUV and small unilamellar vesicles (SUV). However, the therapeutic efficacy of conventional unilamellar or multilamellar liposomes is often limited by low entrapment efficiency and stability issues, which can lead to unintended membrane breaches and premature drug release. Liposomes can be classified as enormous unilamellar vesicles (ULV), multilamellar vesicles (MLV), or unilamellar vesicles (ULV) based on structural features like size and lamellarity. small uni lamellar vesicles (SUV) and large unilamellar vesicles (LUV). However, low entrapment efficiency and stability problems frequently limit the therapeutic efficacy of conventional unilamellar or multilamellar liposomes, which might result in unexpected membrane breaches and early drug release.

Furthermore, the addition of neutral lipids such triolein, tricaprylin, tributyrin, and tributyrine enhances MVLs even more by stabilizing the membrane borders of their distinct multivesicular structure. Hydrophilic medicines can be effectively encapsulated when numerous aqueous vesicles are present. For example, to increase the compound's hydrophilicity and encapsulation effectiveness within the many aqueous MVL vesicles, **Jain et al**. produced MVLs packed with a β-cyclodextrin complex of CXB.

Their investigation found that the CXB encapsulation efficiency in MVLs was an astonishing 88%, which is significantly higher than the 27% attained with ordinary liposomes. Furthermore, 72% of CXB was released over the course of 24 hours, according to drug release experiments, which showed a progressive release profile. Even after 24 hours, a 40% decrease in paw volume in a rat paw edema model demonstrated that

this prolonged release was significantly correlated with improved in vivo anti-inflammatory action. Furthermore, in vivo trials that showed improved efficacy in reducing paw edema supported the benefits of liposomal dexamethasone (DEX) over free DEX.

Proliposomes are a novel drug delivery technology that overcomes some of the drawbacks of conventional liposomes by providing improved stability, simpler sterilization, and protection against drug overload. **Kurakula et al.'s** study examined the efficacy of proliposomes as a delivery mechanism for the anti-inflammatory drug prednisolone. Their formulations were centered on using a thin film hydration process to maximize the concentration of mannitol, lecithin, and cholesterol. The study found that increased phospholipid concentrations were associated with an increase in proliposome yield and drug entrapment efficiency.

Using a dialysis membrane, in vitro drug release experiments showed that PD proliposomal gels produced 50–80% release over 14 hours, while the free drug gel produced 90% release in the same time frame. Rats used in in vivo experiments showed that proliposomes had a 60% reduction in anti-inflammatory activity, while diclofenac gel only showed a 50% reduction. Interestingly, proliposomes outperformed traditional liposomes in terms of stability, suggesting that they could be used in transdermal drug delivery systems.

II. Niosomes

The exploration of vesicular structures, particularly liposomes, for drug delivery has emerged as a prominent focus of scientific inquiry in recent years. While liposomes boast a range of multifunctional characteristics that present considerable promise in therapeutic applications, they are not without limitations. Notable shortcomings include their high formulation costs, instability across diverse pH environments, and a limited shelf life resulting from lipid rancidification. To mitigate these challenges, researchers have turned to niosomes, which represent a favorable alternative. Niosomes are synthesized by substituting the phospholipid components found in liposomes with nonionic surfactants and cholesterol.

Niosomes confer several advantages over their liposomal counterparts. Crucially, they exhibit enhanced chemical stability and are characterized by a extended shelf life, primarily attributable to the use of cost-effective nonionic surfactants. Furthermore, niosomes demonstrate improved permeability for therapeutic agents across the skin barrier, which is particularly advantageous for treating conditions such as rheumatoid arthritis. A growing body of evidence suggests that when niosomes are applied topically, boost drug absorption by lengthening the duration that the stratum corneum and epidermal layers of the epidermis are where medications are stored.

Underlying mechanism for this enhanced absorption appears to be linked to the reduction of transepidermal water loss, which subsequently aids in replenishing the lipids present in the outermost skin layer. This replenishment plays a significant role in smoothing the stratum corneum, thereby promoting easier permeation of drugs. Another notable merit of niosomes lies in their ability to diminish cellular irritation, as these structures do not incorporate charged surfactants. This characteristic stands in stark contrast to vesicles that encapsulate anionic, cationic, or amphoteric surfactants, which are frequently associated with inducing hemolysis or causing cellular irritation.

Nonionic surfactants commonly found in niosomes include alkyl ethers, alkyl glyceryl ethers, sorbitan fatty acid esters such as Span 60, and a variety of polyxethylene fatty acid esters such as Tween 20, 40, and 60. The structural organization of niosomes can be categorized, akin to liposomes, into various types including unilamellar, oligolamellar, and multilamellar niosomes. The formation methodologies for niosomes largely parallel those utilized for liposomes, employing techniques such as lipid film hydration, multiple membrane extrusion, microfluidization, and methods of ethanol and ether injection. The resultant properties of niosomes encompassing size and morphology—are enhanced by multiple factors, such as selection of nonionic surfactants, chosen preparation method, and the temperature during hydration.

Research conducted by Ravalika and her colleagues has shed light on the efficacy of various synthesis methods for niosomes specifically designed to encapsulate the nonsteroidal anti-inflammatory drug etoricoxib. According to their research, niosomes produced using the thin-film hydration approach had a better efficacy than those made using the ether injection method, with an entrapment efficiency of almost 96%. While entrapment efficiency depends on variables including the production technique, the

particular drug, and the surfactants used, niosome size is determined by intricate interactions between the forces that repel, exerted between the bilayers and the drug enclosed within. **Asthana *et al.*** conducted additional research to examine the relationship between cholesterol levels and the size and trapping effectiveness of niosomes. Lower cholesterol concentrations led to smaller niosomal particle sizes, according to their research, It included employing various ratios of Span 60 and cholesterol to encapsulate etodolac into niosomes. On the other hand, larger vesicles formed when the cholesterol level increased; this phenomena is explained by the bilayer membrane's increased hydrophobicity. Remarkably, etodolac entrapment efficiency increased to 95% at cholesterol concentrations between 0.5% and 1%, but decreased at concentrations between 1% and 1.5%. Competitive interactions between cholesterol and etodolac for the restricted packing space within the bilayer are thought to be the cause of this reduction.

The control of drug release from niosomes is significantly influenced by the content of cholesterol. Menshawe and colleagues, for instance, found that niosomes with higher cholesterol levels were linked to a lower drug release rate. Meloxicam This trend is likely due to the increased rigidity imparted to the bilayer by higher cholesterol levels. Additionally, **Fathalla *et al.*,** investigated how the types and concentrations of surfactants affected niosome size, revealing that niosomes formulated with Span 60 produced larger vesicles, approximately 15 µm in diameter, whereas those prepared with Span 20 yielded smaller particles, about 1 µm in diameter. The structural variations between Span 20 and Span 60, with the former having a shorter saturated alkyl chain (C10) and the latter having a longer chain (C16), are the cause of this size discrepancy. Furthermore, vesicular diameter and surfactant concentration were shown to be negatively correlated, This is linked to a drop in free surface energy when the hydrophobicity of surfactants increases.

The release and penetration of therapeutic drugs from niosomes are strongly influenced by the viscosity of the gel formulations utilized for drug delivery. Numerous gel bases, including pluronic F-127, sodium alginate, carbopol 934, sodium carboxymethyl cellulose (NaCMC), and hydroxypropylmethyl cellulose (HPMC), were assessed in a study by **Fathalla et al.** finding that HPMC—with the lowest viscosity (6800 cp)—was the most suitable for use as a gel base. Beyond integrating niosomes into transdermal gels, researchers are also working on the development of transdermal patches incorporating niosomes to enhance applicability and prolong adhesion. For instance, Rajaram and colleagues successfully developed a transdermal patch embedded with a pirfenidone-loaded niosomal gel using PVP, Eudragit L100, and ethyl cellulose. Kinetic studies of drug release from this patch exhibited a zero-order release pattern coupled with non-Fickian diffusion characteristics.

An alternative approach to increase drug delivery efficiency involves the inclusion of permeation enhancers. In their work In order to improve penetration, In order to synthesize niosomes containing diclofenac diethylammonium, Manosroi et al. employed ethanol. Ethanol is known to decrease the melting point of stratum corneum lipids, increasing lipid fluidity and skin permeability. Additionally, ethanol makes niosomes more flexible, which facilitates their passage through the dermal layer's pores. Furthermore, the addition of ethanol to niosomes increases their flexibility, which makes it easier for them to pass through the pores in the dermal layer. These results were further supported by transdermal absorption studies using rat skin, which showed that gels containing elastic niosomes had much higher flux rates—roughly 3.76 µg/(cm² h) for diclofenac—than a commercial gel, which showed only 0.14 µg/(cm² h) under the same experimental conditions. These findings highlight how niosome technology can greatly improve transdermal medication delivery systems.

In advancing our understanding of anti-inflammatory mechanisms, **Alsarra** developed a novel formulation of proniosomes incorporating pirfenidone (PIR). This novel method is based on the notion that a concentrated proniosomal gel can be created by combining alcohol, surfactant, and an aqueous phase. When an excess aqueous phase is introduced, this gel transforms into an effective niosomal dispersion. The study involved various non-ionic surfactants to identify the optimal formulation for niosomes, with a keen emphasis on assessing permeation flux.

When compared to those manufactured with Span 20 and Span 80, the surfactants made with Span 60 demonstrated the best release rate out of the four that

were evaluated: Span 20, Span 60, Span 80, and Tween 80. Additionally, Tween 80's release profile was superior to that of its Span counterparts, most likely due to its enhanced solubility. A remarkable entrapment efficiency of 91.7 ± 2% and a particle size of 4.81 ± 1.1 µm were also obtained by Span 60, which also had the highest phase transition temperature. The study's findings demonstrate that niosomes can significantly boost PIR permeability by altering the stratum corneum, with phospholipids and non-ionic surfactants both acting as effective penetration enhancers.

III. Transferosomes

Transferosomes are an innovative class of vesicular nanoparticles employed in drug delivery via the dermal route, and are developed by the IDEA AG, a German firm. Structurally similar to liposomes, Often called elastic liposomes or ultra-deformable lipids, transferosomes are made expressly to improve the effectiveness of medicinal drug distribution. A lipid bilayer envelops at least one watery compartment within each transferosome. One important feature that distinguishes transferosomes from conventional liposomal formulations is the use of 10–25% edge activators, which are specialized surfactants. These surfactants are essential for giving the transferosomes their elastic qualities, which enable considerable deformation in response to mechanical stress. Span 80, Tween 80, sodium cholate, and sodium deoxycholate are examples of nonsystemic surfactants that are frequently utilized as edge activators.

These compounds, characterized primarily by their single-chained or non-ionic surfactant structures, are integral in destabilizing the lipid bilayer of transferosomes and subsequently reducing interfacial tension. This unique attribute enables transferosomes to deform with minimal energy, which is vital for enhancing dermal penetration of therapeutic agents. The precise control of edge activator concentration is essential, as it substantially influences the elasticity of the vesicles, permitting their shrinkage as they traverse the dermal barrier and allowing them to re-form to their original size upon exit. As a result, transferosomes are capable of penetrating the dermal layers through intracellular lipid or transcellular pathways, significantly enhancing their delivery capabilities.

Transferosomes can encapsulate a wide variety of therapeutic agents, including tiny, moderate, highly hydrophobic, and hydrophilic medicines, thanks to their capabilities that are comparable to those of conventional liposomes. Because of their adaptability, transferosomes have emerged as a viable delivery system for a variety of therapeutic compounds. Anti-cancer medications, corticosteroids, and nonsteroidal anti-inflammatory medicines (NSAIDs), which are used to treat rheumatoid arthritis, have shown particularly good efficacy.

The Swiss regulatory body Swiss Medic approved the commercialization of a transferosome formulation containing the medication ketoprofen in 2007, marking a significant milestone. One of two approaches is usually used to formulate transferosomes: the vortexing-sonication method or the rotary evaporation followed by sonication technique. The rotary evaporation method involves dissolving phosphatidylcholine and certain edge activators in an organic solvent, which is then evaporated to produce a thin layer. After being hydrated with a pharmacological solution and given time to swell, this film is sonicated, which is a procedure similar to that used to create regular liposomes. As an alternative, the vortexing method involves combining the medication, edge activators, and phosphatidylcholine in a phosphate buffer solution., followed by vigorous agitation to yield a milky suspension that is also sonicated. The concentrations of lipids, edge activators, and the organic phase, along with the hydration medium, are critical parameters that affect the resulting size and properties of the transferosomal vesicles.

Research conducted by The impact of several edge activators on transferosomes containing angiotensin-converting enzyme (ACE) was examined by **Dudhipala et al.** In this architecture, sodium deoxycholate, sodium cholate, Tween 80, and Span 80 were employed as edge activators.

, whereas soylecithin and egg lecithin were chosen as lipids.. The physical properties assessed indicated that transferosomes formulated with soylecithin exhibited superior characteristics, with Tween 80 providing the highest degree of flexibility and Span 80 demonstrating the greatest encapsulation efficiency. Notably, sodium deoxycholate and sodium cholate, owing to their bulky, steroid-like structures, resulted in vesicles with reduced flexibility compared to those formulated with the hydrocarbon chains present in Tween 80.

Further advancements in the application of transferosomes are exemplified for topical applications, Sana et al. effectively created transferosomes for the encapsulating of curcumin-tanshinone (CUR TF) and integrated them into a carbopol-934 gel. In comparison to normal curcumin, their results showed that the CUR-TF gel had improved in vitro skin penetration. Corresponding in vivo studies employing a rat model of arthritis corroborated these findings, demonstrating improved treatment efficacy as seen by histological analysis, decreased X-ray scores, and decreased levels of pro-inflammatory cytokines. Additionally, a study by Simoes et al. showed how drug-loaded transferosomes effectively prevented edema from developing in rats' paws. Research by **Sarwa et al.** further examined the formulation of transferosomes combining phosphatidylcholine and Tween 80 for delivering the anti-rheumatic agent capsaicin, showing superior penetration and therapeutic response in vivo when compared to the commercially available Thermagel formulation at equivalent dosages.

Despite their promising applications in topical drug delivery, particularly for conditions such as rheumatoid arthritis, transferosomes do face certain limitations. Challenges such as susceptibility to oxidative degradation, potential phospholipid reorganization, and high manufacturing costs may impede their extensive adoption in clinical practice. Thus, continued research and development in this field remain essential to address these obstacles and fully realize the potential of transferosomes in therapeutic applications.

IV. Ethosomes

Liposomes and niosomes are widely recognized for their capacity to encapsulate drugs and improve their solubility. However, their utility is often limited by their inadequate penetration into the deeper layers of the skin, primarily due to their relatively rigid structures. Ethosomes, on the other hand, emerge as a promising alternative. These lipid-based vesicles are characterized by a higher concentration of ethanol (ranging from 10% to 50%), which imparts a greater degree of flexibility. This unique composition enables ethosomes to traverse the constricted channels within the skin more efficiently, enhancing the fluidity of the lipid matrix. Thus, ethosomes serve as innovative vesicular carriers, substantially enhancing the transdermal delivery of drugs. The combination of ethanol with lipid vesicles not only optimizes their delivery mechanisms but also improves the entrapment efficiency for a variety of pharmaceutical compounds. Ethosomal formulations can be prepared using several techniques, including the hot method, cold method, or classic mechanical dispersion methods. These diverse strategies highlight the versatility of ethosomes in therapeutic applications.

In recent research conducted by Fan et al., ethosomes and liposomes were formulated with tetrandrine, an herbal drug aimed at alleviating symptoms of rheumatoid arthritis (RA). When comparing the two delivery systems, ethosomes demonstrated an average diameter of 78 nm, significantly smaller than the 99 nm average of liposomes. It is believed that the increased ethanol content in the ethosomal formulation modifies the net charge of these systems, aiding in steric stability and causing the ethosomes to shrink. Rat skin was used in penetration tests using a Franz vertical diffusion cell.

illustrated that ethosomes achieved a 2.1-fold increase in transdermal flux for tetrandrine compared to liposomal formulations. Supporting these findings, in vivo studies indicated notable anti-arthritic effects in subjects treated with ethosomes, evidenced by significant reductions in paw edema compared to those receiving liposomal treatment.

Further investigations by **Sakdiset *et al.,*** focused on the stability of ethosomes in comparison to liposomes, concluding that ethosomes offer greater long-term stability. This advantage is attributed to the lack of lipid aggregation, a phenomenon observed in liposomes usually within a week post-formulation. Such aggregation appears to be driven by electrostatic and bonding interactions among the phosphatidylcholine component derived from soybean phosphatidylcholine (SPC) utilized in liposomal formulations, which is less pronounced in ethosomes. Additionally, a study noted that indomethacin-loaded ethosomes at a 20% concentration of ethanol displayed a reduction in vesicular size, whereas an increased concentration of 30% ethanol resulted in an increase in vesicular size, suggesting a shift in the lipid organization within the vesicle membrane.

Separately, **Abdelbary *et al.,*** explored the efficacy of ethosomes in enhancing the transdermal delivery of mometasone furoate (MF). According to their research, ethosomal systems produced skin flux

values that were 2.33 and 3.53 times higher than those of hydroalcoholic solutions and conventional liposomal systems, respectively. The tibiofemoral joint fully recovered after 21 days of consistent application of the ethosomal gel, according to comparative in vivo studies involving various formulations, including ethosomal gel, conventional MF gel, and a commercial formulation in a collagen-induced arthritis (CIA) model. **Sarwar *et al***. also reported much better permeation rates for ethosomal capsaicin (CAP) vesicles, surpassing results with hydroethanolic solutions and the commercial product Thermagel, with a flux rate of 15 cm/h × 10–3 after 24 hours in a modified diffusion cell.

Confocal laser scanning microscopy confirmed the results, showing that capsaicin-loaded vesicles successfully crossed the epidermal barrier. Consistent outcomes were confirmed in a collagen-induced arthritis model, where ethosomal capsaicin reduced paw edema by 40% but Thermagel only reduced it by 15%.

Transfereosomes represent an advanced iteration of vesicular carriers, sharing similarities with ethosomes but enhanced by the incorporation of edge activators, particularly surfactants. This enhancement significantly increases their elasticity by lowering the elastic modulus. The potential of formulating hybrid systems that integrate the characteristics of both transfereosomes and ethosomes presents exciting opportunities in the realm of transdermal drug delivery. A pioneering study by Garg et al. successfully developed transethosomes that encapsulated the anti-inflammatory compound pirfenidone (PIR), utilizing Span 80 as the edge activator. Through the application of a membrane extrusion technique, they assessed the deformability index and elasticity of these drug-loaded transethosomes. Their results revealed that the transethosomal formulation could navigate openings 12.73 times smaller than its actual size, indicating superior elasticity when compared with liposomes and ethosomes. This enhanced elasticity contributed to significant dermal penetration, supported by ex vivo permeation studies that demonstrated Compared to other gel formulations, transethosomal formulations have the highest medication penetration into pig skin.

In line with a growing trend toward targeted drug delivery, researchers have been investigating various strategies to optimize the release profiles and therapeutic efficacy of pharmaceuticals. This includes approaches such as conjugation with targeting ligands and the design of stimuli-responsive delivery systems. Targeting reactive oxygen species (ROS) found in inflammatory areas can have major therapeutic benefits in rheumatoid arthritis (RA), which provides a relevant background for our efforts. In a notable work, Song et al. used the antioxidant ascorbic acid to functionalize the surface of transethosomes loaded with sinomenine hydrochloride (SIN-HCl). The purpose of this tactical change was to improve SIN-HCl localization in inflammatory areas through redox interactions when ROS levels were elevated. These transethosomes were shown to have a transdermal permeability that was 98% higher than that of conventional ethosomes, which represents a major breakthrough in targeted delivery methods for anti-inflammatory medications.

In a different study on vascular uptake, **Chourasia et al.** looked at how ethosomes might improve the topical administration of ketoprofen (KET), a nonsteroidal anti-inflammatory medication that has long been known to have poor transdermal penetration despite a number of enhancement techniques.

The researchers developed ethosomes that entrapped KET within phosphatidylcholine lipid bilayers using an ethanolic core. Their formulations yielded ethosomes with particle sizes ranging from 362.5 to 406.3 nm, formulated with phosphatidylcholine concentrations of 2.5-3% (w/v) and ethanol concentrations of 20-25% (v/v). An entrapment efficiency of 73% was achieved, attributable to the increased solubility of the drug in ethanol. Collectively, these studies underscore the significant advancements in the development and application of ethosomal systems and their derivatives, paving the way for novel therapeutic formulations aimed at improving drug delivery and efficacy in various clinical contexts.

The investigation into the interactions between phosphatidylcholine and ethanol has revealed a nuanced relationship that influences drug release dynamics. It was found that an increased proportion of phosphatidylcholine tends to slow the release of drugs, whereas a higher concentration of ethanol significantly accelerates this process. The 24-hour release study demonstrated a substantial cumulative drug release of 81.4±5%. The increased fluidity of the bilayer membrane as a result of elevated ethanol levels is the main cause of this increased release rate.

According to a comparative study of transdermal flow profiles, the ethosomal formulation with 40% ethanol and 1% phosphatidylcholine had the highest penetration rates. On the other hand, transdermal fluxes were significantly reduced in formulations with lower ethanol contents. This finding implies that the alcohol concentration is essential for promoting lipid interactions in the stratum corneum, which in turn increases the permeability of the skin. Moreover, it was shown that the interactions between the ethosomal formulation and skin lipids influenced the drug release mechanisms.

Vijayakumar examined the transdermal delivery potential of diclofenac potassium, a hydrosoluble anti-inflammatory medication renowned for its nearly total gastrointestinal absorption and substantial first-pass metabolism in the liver, as an extension of this discussion on transdermal delivery techniques.

The adverse effects associated with oral administration, such as severe gastrointestinal complications including ulceration and potential bleeding, warrant the exploration of alternative delivery methods to enhance therapeutic efficacy while minimizing risks. The ethosomal formulation developed featured phosphatidylcholine and ethanol with diclofenac potassium incorporated at a concentration of 1% (w/w), utilizing a mechanical dispersion technique. Different formulations showed varying entrapment efficiencies, ranging from 18.74% to 72.91%. The highest efficiency was attained at 4% (w/v) phosphatidylcholine and 40% (v/v) ethanol concentrations.

An inverse relationship was established between vesicular size and ethanol concentration, while larger vesicular sizes were associated with increased phospholipid concentrations. Notably, the enhancements in both ethanol and phospholipid content led to improved entrapment efficiencies, resulting in a cumulative drug release of 60.37% from the ethosomal formulation, in stark contrast to the 15.95% release observed with liposomal formulations.

Moreover, skin permeation studies indicated that ethosomes facilitate a fourfold increase in permeation compared to traditional liposomes. Carbopol 980 served as the gelling agent in this formulation, and the in vivo anti-inflammatory effectiveness was assessed through percentage inhibition, which indicated a remarkable 44.44% inhibition rate for the ethosomal gel, compared to 35.80% for a marketed formulation after four hours of application. When taken as a whole, our results highlight the potential of ethosomes as a better diclofenac potassium delivery mechanism, exhibiting both improved anti-inflammatory properties and increased penetration.

Table 2 : Features of Nanocarriers used in the Management of Rheumatoid Arthritis.
(Jeniffer *et al.*,2025)

System	Carrier	Features
A.Lypophillic System	**I.Nanoemulsion**	Nanoemulsions (NEs) are defined as clear colloidal dispersions, with particle sizes generally measuring between 10 to 200 nanometers This unique characteristic allows for the formulation of diverse dosage forms such as sprays, foams, creams, and gels, thereby significantly broadening their applicability in both pharmaceutical and cosmetic industries
	II. Solid lipid Nanoparticle	The spherical structure of solid lipid nanoparticles (SLNs) ranges from 50 to 1000 nanometers in diameter. The amphiphilic properties of these phospholipids significantly enhance the transdermal absorption of both hydrophilic and lipophilic pharmaceutical agents Moreover, SLNs exhibit a higher entrapment efficiency for lipophilic substances than do liposomes, a feature that can be largely attributed to their solid lipid matrix, which affords a more stable environment for drug incorporation.
B.Vesicular System	**I. Liposome**	Phospholipid vesicles with one or more concentric lipid bilayers make up liposomes.

		These membranes encapsulate hydrophobic molecules within their lipid layers, while hydrophilic substances reside in the aqueous core. This unique structure renders liposomes a versatile platform for effective drug delivery applications
	II. Niosome	Niosomes are self-assembled bilayer structures formed from nonionic surfactants in an aqueous environment, with cholesterol as their primary lipid component. This unique composition facilitates the sustained and controlled delivery of therapeutics, enhancing targeting efficiency to specific sites.
	III.Transferosome	A lipid bilayer with an edge activator identifies the ultra-deformable vesicles called transferosomes. Principal component of lipid, phosphatidylcholine is abundantly found in cell membranes, which enhances its compatibility with human skin and reduces the potential for hypersensitivity reactions..
	IV. Ethosome	Ethosomes are tiny vesicles made mainly of phospholipids and packed with a good amount of ethanol, usually between 20 to 45%. The ethanol not only helps the vesicles move better through the skin but also makes them more flexible.

(**Jeniffer *et al.*,2025)**

6. Patents for Rheumatoid Arthritis Treatment

Between 2015 and 2025, it is anticipated that the prevalence of rheumatoid arthritis (RA) would rise in eight major economies: the United States, France, Germany, the United Kingdom, Spain, Italy, Brazil, Australia, and Japan, according to a recent study. Epidemiologists predict that the number of RA cases will grow at an annual rate of 1.36%, increasing from over 6.1 million in 2015 to almost 7 million by 2025. Notably, about 45.9% of all RA cases in 2015 were reported in the United States. The complexity of RA treatments has led to many clinical trials and a wave of new patent applications in the US and the other significant economies mentioned. A search of the Google Patents database reveals that most RA-related patents are based on terms like topical treatment and nano-formulation. The patents are mainly granted in countries like the US, Canada, India, Japan, Australia, and across Europe. On a more cautionary note, long-term use of RA medications such as biologicals, DMARDs, NSAIDs, and corticosteroids—can lead to issues like osteoporosis, stomach ulcers, and poor wound healing. Furthermore, these medications can affect liver and kidney functions, making treatment a bit tricky. To tackle these problems, researchers are striving to create new delivery systems, particularly through the development of nanocarriers. These innovative solutions can penetrate the skin effectively when used topically, ensuring that medications are delivered directly to the affected joints with less risk of side effects. This method not only targets the inflammation more accurately but also reduces the overall medication dosage, which is especially beneficial for high-risk patients.

7. Conclusion:

Disease-modifying antirheumatic medications (DMARDs), corticosteroids, biologics, and Non-steroidal anti-inflammatory drugs (NSAIDs) are among pharmacological treatments that must be continuously administered in order to manage rheumatoid arthritis (RA). Although these therapies have demonstrated efficacy in reducing inflammation and managing symptoms, extended use of them raises serious concerns about side effects.

These side effects could include immunosuppression, liver and renal malfunction, peptic ulcers, osteoporosis, decreased wound healing, and stomach discomfort, liver and renal malfunction, peptic ulcers, osteoporosis, decreased wound healing, and stomach discomfort. Given these potential complications, the advancement of treatment strategies toward site-specific drug delivery becomes imperative, as it seeks to minimize systemic exposure and mitigate side effects.

Recent innovations in topical drug delivery systems have fostered the development of nanocarriers. These engineered nanoparticles are designed to penetrate the skin layers effectively when applied topically. Nanocarriers represent a promising avenue for localized drug delivery to inflamed

joints, which not only enhances therapeutic effectiveness but also allows for reduced dosages and a lower incidence of off-target effects. This targeted approach is particularly advantageous for high-risk populations who may be more susceptible to the adverse outcomes associated with conventional systemic therapies.

Among the various types of nanocarriers, lipophilic carriers and vesicular systems, including nanoemulsions and solid lipid nanoparticles, have illustrated considerable promise in achieving targeted drug delivery to affected tissues. By making weakly water-soluble medications more soluble, these lipophilic carriers improve drug loading and stability and allow for lower dosage schedules. Furthermore, liposomes, known for their versatility in composition, surface modification, and drug encapsulation capabilities, have significant potential; however, they are susceptible to degradation due to lipid oxidation.

In contrast, niosomes present a viable alternative to liposomes, as they are composed of surfactants that confer greater stability. Like Niosomes and liposomes offer advantageous properties for drug delivery, including prolonged drug release and high drug loading efficiency.

Nonetheless, careful scrutiny of the surfactants used in their formulation is necessary, as their toxicological thresholds must be considered. Transfersomes, which exhibit structural similarities to liposomes, incorporate specialized surfactants that grant them elastic and ultradeformable properties; These properties can greatly increase the cutaneous penetration of therapeutic compounds that are poorly soluble. Ethosomes present yet another possibly safer option for topical distribution since they incorporate ethanol within their membrane structure. Despite studies demonstrating the inherent stability of these vesicular systems, there remains concern over incidents of membrane rupture that could lead to premature drug release and unintended off-target effects. Comparatively, solid lipid nanoparticles showcase superior stability, which is vital for preserving the therapeutic integrity of the encapsulated drug. Numerous studies show that different carrier systems improve skin penetration and accomplish targeted cutaneous administration, depending on the delivery vehicle's composition as well as the physicochemical characteristics of the active ingredients. The pharmaceutical industry has used a variety of tactics to solve issues with drug absorption and penetration through the skin barrier. These include applying chemical enhancers, strategically placing nanocarriers, and altering the stratum corneum by hydrating to improve penetration. The effectiveness of chemical penetration enhancers such as isopropyl myristate, oleyl alcohol, propylene glycol, and triacetin in facilitating epidermal barrier penetration is significantly influenced by the physicochemical characteristics of the active compounds. These characteristics include molecular weight, melting point, charge, lipophilicity, and shape.

Thus, for the development of novel dermatological formulations, comprehensive investigations are required to identify the most suitable penetration enhancers or formulations that will achieve the desired dermal delivery.

Manipulating molecular characteristics or judiciously selecting an appropriate delivery system be it through penetration enhancement or via nanocarriers can optimize drug penetration through specified pathways. A profound understanding of potential routes for skin penetration is crucial to identifying the most efficient system for administering therapeutic agents at their intended site. Employing a combinatory approach that integrates both permeability enhancers and nanocarriers may significantly bolster drug permeation efficacy while concurrently reducing the required active concentrations compared to isolated methods. In the field of topical applications, the difficulty of safely and effectively overcoming the skin barrier whether by chemical, physical, or nanotechnological means remains a crucial factor. As advancements in our understanding of these innovative delivery systems continue to emerge, the prospect of employing colloidal nanocarriers in the management of rheumatoid arthritis becomes increasingly tangible. Additionally, continued research into cutting-edge formulations like self-emulsifying delivery methods, nanoparticles, nanogels, and nanostructured lipid carriers suggests that RA therapy approaches are evolving dynamically.

Looking ahead, the anticipated development of new DMARDs and biological DMARDs tailored for the treatment of RA and associated chronic inflammatory conditions promises to yield significant clinical advancements. These innovative nanoformulations possess the potential to transition into clinical trials, underscoring their capacity to

reduce dosage requirements and administration frequency, as well as to lessen associated side effects. These patterns have the potential to significantly improve the lives of those who suffer from rheumatoid arthritis.

8. References :

1. Huang J, Fu X, Chen X, Li Z, Huang Y, Liang C. Promising therapeutic targets for treatment of rheumatoid arthritis. Frontiers in immunology. 2021 Jul 9;12:686155.
2. Kumar LD, Karthik R, Gayathri N, Sivasudha T. Advancement in contemporary diagnostic and therapeutic approaches for rheumatoid arthritis. Biomedicine & Pharmacotherapy. 2016 Apr 1;79:52-61.
3. Savithramma N, Yugandhar P, Devi PS, Ankanna S, Suhrulatha D, Prasad KS, Ranjani R, Nagaraju N, Chetty KM. Documentation of ethnomedicinal information and antimicrobial validation of Thespesia populnea used by Yanadi tribe of Ganugapenta village, Chittoor district, Andhra Pradesh, India. Journal of intercultural ethnopharmacology. 2017 Apr 11;6(2):158.
4. Dubey D, Kumar S, Chaurasia S, Guleria A, Ahmed S, Singh R, Kumari R, Modi DR, Misra R, Kumar D. NMR-based serum metabolomics revealed distinctive metabolic patterns in reactive arthritis compared with rheumatoid arthritis. Journal of proteome research. 2018 Oct 17;18(1):130-46.
5. Geng Y, Fan Y, Wang Y, Deng X, Ji L, Zhang X, Song Z, Huang H, Gui Y, Zhang H, Sun X. Flare and change in disease activity among patients with stable rheumatoid arthritis following coronavirus disease 2019 vaccination: a prospective Chinese cohort study. Chinese Medical Journal. 2023 Oct 5;136(19):2324-9.
6. Guo C, Fu R, Wang S, Huang Y, Li X, Zhou M, Zhao J, Yang N. NLRP3 inflammasome activation contributes to the pathogenesis of rheumatoid arthritis. Clinical & Experimental Immunology. 2018 Nov;194(2):231-43.
7. Chando A, Basudkar V, Gharat S, Momin M, Khan T. Development and preclinical assessment of nanoemulgel loaded with phytoconstituents for the management of rheumatoid arthritis. Drug Delivery and Translational Research. 2024 Feb;14(2):524-41.
8. Nash TE, Ware JM, Coyle CM, Mahanty S. Etanercept to control inflammation in the treatment of complicated neurocysticercosis. The American journal of tropical medicine and hygiene. 2019 Jan 2;100(3):609.
9. Pirmardvand Chegini S, Varshosaz J, Taymouri S. Recent approaches for targeted drug delivery in rheumatoid arthritis diagnosis and treatment. Artificial cells, nanomedicine, and biotechnology. 2018 Nov 5;46(sup2):502-14.
10. Shaji A, Pradeep E, Kumar KA, Kumar SD, Mohideen S, Ashwin VY. Comparative Study of Functional Outcome of Intra-articular Injection of Platelet-Rich Plasma versus Corticosteroid in Treatment of Osteoarthritis of Knee. Journal of Orthopaedic Case Reports. 2025 Apr;15(4):287.
11. Higaki M, Ishihara T, Izumo N, Takatsu M, Mizushima Y. Treatment of experimental arthritis with poly (D, L-lactic/glycolic acid) nanoparticles encapsulating betamethasone sodium phosphate. Annals of the rheumatic diseases. 2005 Aug 1;64(8):1132-6.
12. Lala V, Tikly M, Musenge E, Govind N. Comorbidities in Black South Africans with established rheumatoid arthritis. International Journal of Rheumatic Diseases. 2022 Jun;25(6):699-704.
13. Shakeel L, Shaukat A, Khaliq N, Kashif A, Mujeeb A, Adnan Z, Taj J, Akilimali A. Rheumatoid arthritis: a comprehensive overview of genetic markers, emerging therapies, and personalized medicine. Annals of Medicine and Surgery. 2025 Feb 1;87(2):696-710.
14. El Leithy SA, Metwaly MM, Hassan RF, Thabet RN, Rashad SM. Carpal Tunnel Syndrome in Rheumatoid Arthritis: Assessment of Different Anatomical Causes in Non-Clinically Deformed Wrist. The Egyptian Journal of Hospital Medicine (July 2023).;92:6706-11.
15. Pathan E, Gaitonde S, Rajadhyaksha S, Sule A, Mittal G, Joshi VR. A longitudinal study of serum creatinine levels in patients of

rheumatoid arthritis on long term NSAID therapy. JOURNAL-ASSOCIATION OF PHYSICIANS OF INDIA. 2003 Nov 1;51:1045-51.

16. Chandra PE, Sokolove J, Hipp BG, Lindstrom TM, Elder JT, Reveille JD, Eberl H, Klause U, Robinson WH. Novel multiplex technology for diagnostic characterization of rheumatoid arthritis. Arthritis research & therapy. 2011 Jun 24;13(3):R102.
17. Tiwari L, Nigam N, Sachan AK, Dhakad U, Kumar P, Rao CV, Shukla S. The Role of Synovitis and Latent Transcription Factors in the Pathogenesis of Rheumatoid Arthritis. Current Rheumatology Reviews. 2025 Apr 15.
18. Shrivastava S, Bahuguna T, Mondal S, Kumar S, Mathew B, Jeengar MK, Naidu VG. Attenuation of adjuvant-induced arthritis with carnosic acid by inhibiting mPGES-1, COX-2, and bone loss in male SD rats. Immunopharmacology and Immunotoxicology. 2024 Jul 3;46(4):538-49.
19. Pleguezuelos-Villa M, Nácher A, Hernández MJ, Buso MO, Sauri AR, Díez-Sales O. Mangiferin nanoemulsions in treatment of inflammatory disorders and skin regeneration. International journal of pharmaceutics. 2019 Jun 10;564:299-307.
20. Valikhani M, Kavand S, Toosi S, Kavand G, Ghiasi M. ABO blood groups, rhesus factor and pemphigus. Indian Journal of Dermatology. 2007 Oct 1;52(4):176-8.
21. Khan A, Salim B, Perveen S, Samreen S, Gul H, Nasim A. Overcoming rheumatoid arthritis challenges: Ensuring timely referral to rheumatologists in resource-scarce countries. Rheumatology and Immunology Research. 2023 Dec 19;4(4):222-4.
22. Jain S, Dhir V, Aggarwal A, Gupta R, Leishangthem B, Naidu S, Khullar A, Maurya S, Dhawan V, Sharma SK, Sharma A. Comparison of two dose escalation strategies of methotrexate in active rheumatoid arthritis: a multicentre, parallel group, randomised controlled trial. Annals of the Rheumatic Diseases. 2021 Nov 1;80(11):1376-84.
23. Pham CV, Van MC, Thi HP, Thanh CĐ, Ngoc BT, Van BN, Le Thien G, Van BN, Nguyen CN. Development of ibuprofen-loaded solid lipid nanoparticle-based hydrogels for enhanced in vitro dermal permeation and in vivo topical anti-inflammatory activity. Journal of Drug Delivery Science and Technology. 2020 Jun 1;57:101758.
24. Prasad P, Verma S, Surbhi, Ganguly NK, Chaturvedi V, Mittal SA. Rheumatoid arthritis: advances in treatment strategies. Molecular and cellular biochemistry. 2023 Jan;478(1):69-88.
25. Chaudhari K, Rizvi S, Syed BA. Rheumatoid arthritis: current and future trends. Nature reviews Drug discovery. 2016 May;15(5):305-6.
26. Mendoza-Muñoz N, Leyva-Gómez G, Piñón-Segundo E, Zambrano-Zaragoza ML, Quintanar-Guerrero D, Del Prado Audelo ML, Urbán-Morlán Z. Trends in biopolymer science applied to cosmetics. International Journal of Cosmetic Science. 2023 Dec;45(6):699-724.
27. Bhalekar M, Dubey S. Drug delivery systems for rheumatoid arthritis treatment. InPhotophysics and Nanophysics in Therapeutics 2022 Jan 1 (pp. 311-326). Elsevier.
28. Mohammadi F, Vosough A, Tanideh N, Mohammadi Samani S, Ahmadi F. Hyaluronic acid scaffolds and injectable gels for healing of induced arthritis in rat knee: effect of prednisolone revisited. Regenerative Engineering and Translational Medicine. 2021 Sep;7(3):393-404.
29. Vidjaya S, Valentinovich YA. Soluble molecules of immunoglobulins superfamily in rheumatoid arthritis. Медицинский вестник Северного Кавказа. 2017;12(3):256-60.
30. Chandra KR, Kumar BJ, Taj DM, M P, Devaki K, Shekhar NR, Kommireddy S, Chittipolu AK, Yerrakula G. Effect of Coping Strategies on Pain Intensity in Patients with Rheumatoid Arthritis. Journal of Pharmacology and Pharmacotherapeutics. 2024 Sep;15(3):277-83.

31. Jain S, Dhir V, Aggarwal A, Gupta R, Leishangthem B, Naidu S, Khullar A, Maurya S, Dhawan V, Sharma SK, Sharma A. Comparison of two dose escalation strategies of methotrexate in active rheumatoid arthritis: a multicentre, parallel group, randomised controlled trial. Annals of the Rheumatic Diseases. 2021 Nov 1;80(11):1376-84.
32. Sun Y, Gao L, Kan Y, Shi BX. The Perceived Stress Scale-10 (PSS-10) is reliable and has construct validity in Chinese patients with systemic lupus erythematosus. Lupus. 2019 Feb;28(2):149-55.
33. Silvagni E, Di Battista M, Bonifacio A, Zucchi D, Governato G, Scire C. One year in review 2019: novelties in the treatment of rheumatoid arthritis. Clinical and experimental rheumatology. 2019;37(4):519-34.
34. Fathalla BM, Alsarhan A, Afzal S, El Naofal M, Abou Tayoun A. The genomic landscape of pediatric rheumatology disorders in the Middle East. Human Mutation. 2021 Apr;42(4):e1-4.
35. Dudhipala N, Phasha Mohammed R, Adel Ali Youssef A, Banala N. Effect of lipid and edge activator concentration on development of aceclofenac-loaded transfersomes gel for transdermal application: in vitro and ex vivo skin permeation. Drug development and industrial pharmacy. 2020 Aug 2;46(8):1334-44.
36. Anchan R, Ghadi A, Chauhan MA, Godad A, Gharat S. Understanding the role of ethosomes in rheumatoid arthritis: innovative solutions to challenges in transdermal delivery of synthetic drugs and phytoconstituents. Journal of Drug Targeting. 2025 Mar 8:1-5.
37. Goma SH, Razek MR, Abdelbary NM. Impact of rheumatoid arthritis on the quality of life and its relation to disease activity. Egyptian Rheumatology and Rehabilitation. 2019 Oct;46(4):304-12.
38. Khan MA, Sarwar AH, Rahat R, Ahmed RS, Umar S. Stigmasterol protects rats from collagen induced arthritis by inhibiting proinflammatory cytokines. International Immunopharmacology. 2020 Aug 1;85:106642.
39. Vijayakumar D, Suresh K, Manoharan S. Lipid peroxidation and antioxidant status in blood of rheumatoid arthritis patients. Indian journal of clinical biochemistry. 2006 Mar;21(1):105-.
40. Fechtner S, Singh A, Chourasia M, Ahmed S. Molecular insights into the differences in anti-inflammatory activities of green tea catechins on IL-1β signaling in rheumatoid arthritis synovial fibroblasts. Toxicology and applied pharmacology. 2017 Aug 15;329:112-20.
41. Alarcon JF, Karusan NR, Presciutti C, Miras J, Magana JR, Guerra-Rebollo M, Borrós S, Ahmad N, Fornaguera C. Revolutionizing rheumatoid arthritis therapy: the potential of lipid nanocarriers. RSC advances. 2025;15(33):27388-402.
42. Ashiq K, Ashiq S, Mobashar A, Abid F, Yasmeen A, Shehzadi N, Khan MT, Hussain K. An updated review on rheumatoid arthritis (RA): epidemiology, pathophysiology, diagnosis, and the current approaches for its treatment. Sudan Journal of Medical Sciences. 2023;18(4):539-

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