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Topical nanocarriers for management of Rheumatoid Arthritis: A review

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ABSTRACT

Rheumatoid arthritis (RA) is a systemic autoimmune disease manifested by chronic joint inflammation leading to severe disability and premature mortality. With a global prevalence of about 0.3%–1% RA is 3–5 times more prevalent in women than in men. There is no known cure for RA; the ultimate goal for treatment of RA is to provide symptomatic relief. The treatment regimen for RA involves frequent drug administration and high doses of NSAIDs such as indomethacin, diclofenac, ibuprofen, celecoxib, etorcoxib. These potent drugs often have off target effects which drastically decreases patient compliance. Moreover, conventional non-steroidal anti-inflammatory have many formulation challenges like low solubility and permeability, poor bioavailability, degradation by gastrointestinal enzymes, food interactions and toxicity. To overcome these barriers, researchers have turned to topical route of drug administration, which has superior patience compliance and they also bypass the first past effect experienced with conventional oral administration. Furthermore, to enhance the permeation of drug through the layers of the skin and reach the site of inflammation, nanosized carriers have been designed such as liposomes, nanoemulsions, niosomes, ethosomes, solid lipid nanoparticles and transferosomes. These drug delivery systems are non-toxic and have high drug encapsulation efficiency and they also provide sustained release of drug. This review discusses the effect of formulation composition on the physiochemical properties of these nanocarriers in terms of particle size, surface charge, drug entrapment and also drug release profile thus providing a landscape of topically used nanoformulations for symptomatic treatment of RA.

1. Introduction

Rheumatoid Arthritis (RA) is a chronic systemic autoimmune inflammatory disease characterized by inflammation of the synovial membrane, which leads to progressive destruction of articular cartilage, bone erosion and related deformities [1]. It is manifested as warm, swelling, tenderness experienced in the joints and is also accompanied with loss of motion and grip strength due to synovial hyperplasia and pannus formation [2,3]. According to WHO reports, RA is mostly diagnosed during productive years of adulthood i.e. ages 20–40, which hampers the quality of life [4]. Recent epidemiological analysis demonstrates the prevalence of RA in developed countries is about 0.3–1% and is experienced more women by (4%) than by men (2%). Within 10 years of onset of RA, more than 50% patients in developed countries discountined from a full time job [5]. Every year out of every 100,000 people, 41 people are diagnosed with RA and around 1.3 million Americans are diagnosed with RA. The disease may be diagnosed as early as three months from onset of disease to two years when its established and become more significant [2].

Development of new diagnostic tools for detection of antibodies and novel cytokine therapies have contributed to a deeper understanding of the pathogenesis of RA. However; the exact etiology still remains unknown. The synovial inflammation experienced by the patients is characterized by infiltration of T lymphocytes and macrophages along with B cells and dendritic cells. Additionally, synovial fibroblasts (SFs) proliferation along with the secretion of proteolytic enzymes may further lead to irreversible cartilage and bone destruction, if left untreated [6].

The onset of RA is thought to be due to a combination of environmental and/or genetic factors such human leukocyte antigen (HLA). Cytokines and T-cell signalling plays a crucial role in progression of RA. The synovial inflammation and articular destruction associated with RA is characterized by elevated levels of pro-inflammatory cytokines such as interluekin-6 (IL-6), interluekin-1β (IL-1β), nuclear factor-κB (NF-κB), fibroblasts and tumor necrosis factor-α (TNF-α) along with prostaglandin E2 (PGE2) and nitric oxide (NO), [2,7–10]. The levels of

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pro-inflammatory cytokines are observed to be predominantly high as compared to anti-inflammatory cytokines in the plasma of RA patients, which further activates other cytokines and matrix metalloproteinases (MMPs) associated with cartilage and bone destruction. Interluekin-1 (IL-1) is one of the primary pro-inflammatory cytokines secreted by synovial macrophages, which plays significant role in progression of RA by exerting multiple biological effects such as synthesis of collagenase, prostagladins, stimulation of fibroblasts, and chemotaxis for B and T cells [11]. TNF-α is another important cytokine, which is abundantly found in the rheumatoid joints as well as circulation and stimulates PGE2 and collagenase, induces bone resorption, inhibits bone formation and production of MMPs [12]. During the progression of inflammation, the synovium thickens and differentiation of osteoclasts increases, due to which cartilage and underlying bones begin to disintegrate, leading to joint destruction (Fig. 1). Therefore, NF-κB and pro inflammatory cytokines serve as potential targets for treatment of RA [13]. Currently, there is no known cure or means of preventing RA, therefore early diagnosis and treatment is required to maintain productive and normal active life [14].

2. Current treatment strategies for Rheumatoid Arthritis

The main aim and strategy for the management of rheumatoid arthritis is to decrease the joint inflammation and pain, maximize the joint function and to prevent the deformity and joint destruction [15, 16]. Ministry of Health and Family Welfare, Government of India has issued the Standard Treatment Guidelines for Rheumatoid Arthritis which are outlined in Fig. 2. The current approaches used for treatment of RA in India are the non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids, disease modifying anti-rheumatic drugs (DMARDs), biological DMARDs prevent the joint damage.

Similar treatment protocol is used in countries like USA and Europe. The American college of rheumatology (ACR) and European league against rheumatism (EULAR) publish periodic recommendations for optimum treatment of RA for USA and European regions. The ACR has published new guidelines in 2015 regarding use of DMARDs and biologic DMARDs and glucocorticoids in high-risk populations i.e., patients with hepatitis, congestive heart failure, malignancy, and other serious infections. The use of vaccines in patients starting/receiving DMARDs or biologics and use of biologics in patients with concomitant tuberculosis (TB) [17]. Both ACR and EULAR suggest methotrexate (MTX) as the first line therapy. They also recommend biologic agents such as TNFi to be added for patients whose severity of disease remains moderate or high even after treatment with DMARDs or for those who exhibit insufficient responses to MTX [18]. Additionally, EULAR also recommends MTX as combination therapies with other DMARDs or glucocorticoids. In such cases dose escalation should be done within 4–6 weeks to reach a weekly dose of about 0.3 mg per kg. If contraindications or intolerance to MTX is observed, leflunomide or sulfasalazine can be considered as part of first-line treatment strategy. In absence of clinical relief from RA after at least two conventional synthetic DMARDs, a biologic DMARD or a targeted synthetic DMARD is added to the treatment regimen as secondary treatment strategy [19]. Patient preference, cost and tolerance is the deciding factor while designing such combination therapy. Interleukin-6 pathway inhibitors can also be used as co-medication. Patients with persistent remission require tapering biologic DMARDS or targeted synthetic DMARDs, especially when these therapies are combined with a conventional synthetic DMARDs. Sudden discontinuation of biologic DMARDs is often result in flares and may aggravate the disease. In all cases, the treatment decisions should be made by the physicians in conjunction with patients through a mutual decision making process considering the patient's severity of disease, tolerance, financial preference and comorbidities [20]. Table 1 describes various dosage form used in management of RA and also describes the mechanism of action of each class of drug.

3. Need for novel nanocarriers in Rheumatoid Arthritis

The early diagnosis and identifying the onset of RA is crucial in maintaining a productive and normal active lifestyle [1,14]. The conventional treatment approaches for RA mainly includes administration of first line drugs such as non-steroidal anti-inflammatory drugs (NSAIDs) and glucocorticosteroids (GCs), are mainly used for the suppression of pain [34]. Commonly used NSAIDs are indomethacin (IND), celecoxib (CLX), etoricoxib (EXB), meloxicam (MLX), etc which act by inhibiting the inflammatory COX enzyme [35–38]. However, chronic use of NSAIDs result in side effects like gastrointestional bleeding and perforation, hypertension, myocardial infarction and nephrotoxicity [39]. GCs represent the most important class of anti-inflammatory drugs for management of inflammation and pain associated to RS. However, prolonged usage of GCs may lead to side effects such as muscle atrophy, osteoporosis, suppression of hypothalamic-pitutary-adrenal axis, glaucoma, diabetes, etc [40–43]. Disease modifying antirheumatic drugs (DMARDs) are second line agents which control and decrease joint damage [15,44]. Methotrexate (MTX) [45], sulfasalazine [46], clodronate [47], leflunomide (LFU) [48], D-penicillinamine [49], cyclosporine

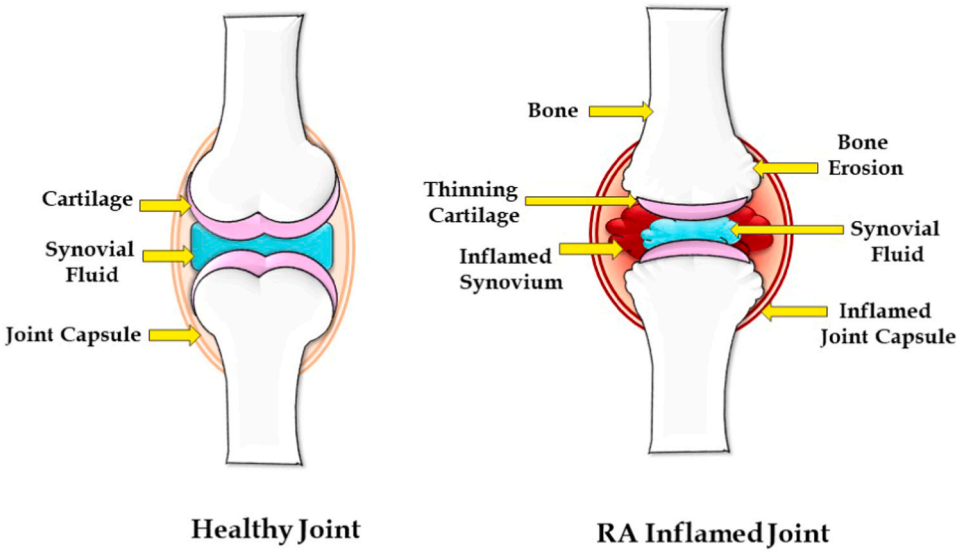

Fig. 1. Comparision between a healthy joint and RA affected.

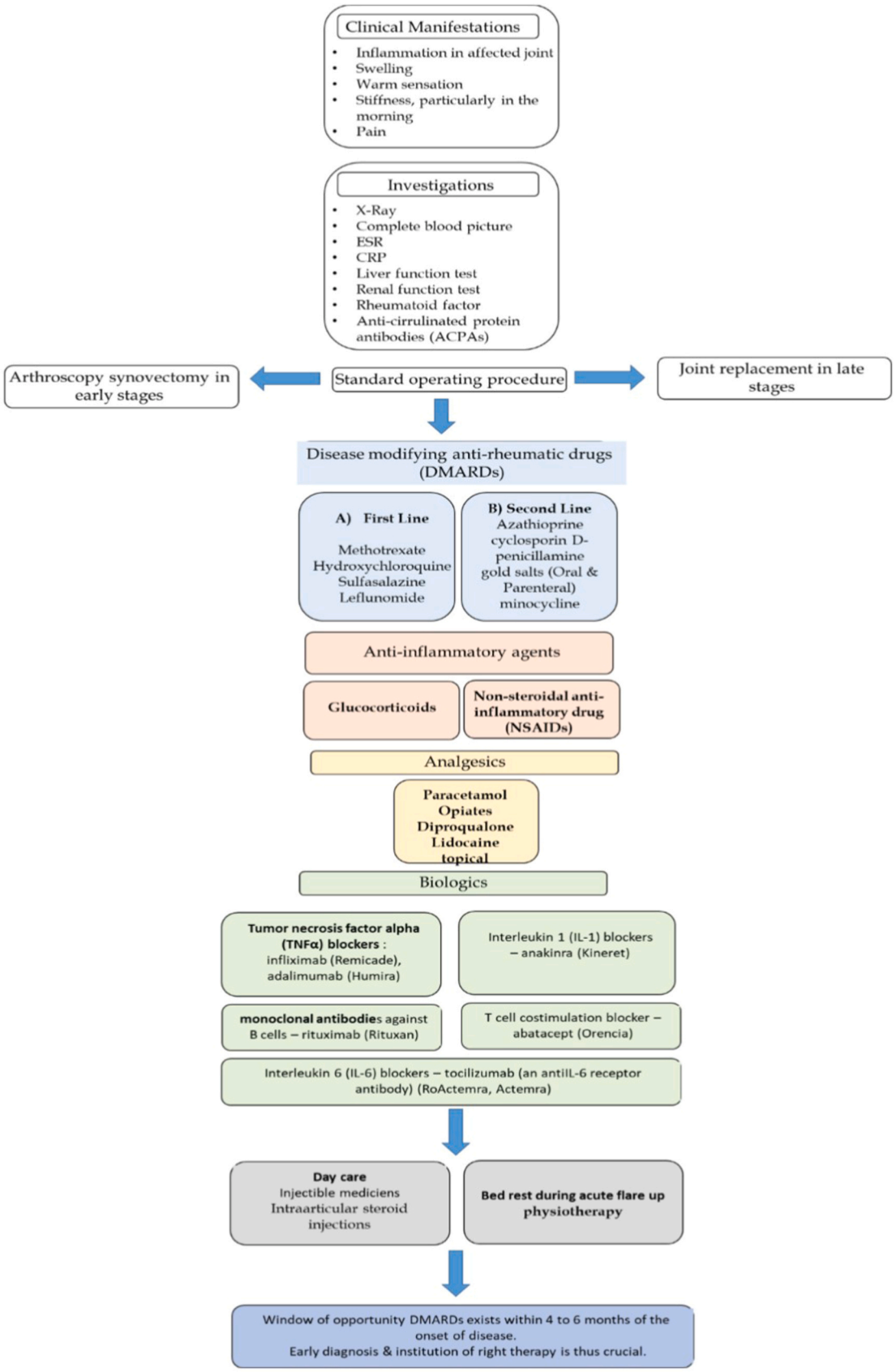

Fig. 2. Current treatment strategy for Rheumatoid Arthritis in India.

Table 1
Current therapy for management of Rheumatoid Arthritis.

Sr. No	Dosage form	Class of Drug	Drug	Mechanism of Action	Brand name	Manufacturer	Ref.
1.	Tablets	NSAIDs	Celecoxib	Selective inhibiton of COX-2	Celebrex	G.D Searle	[21]
			Nabumeton	Selective inhibiton of COX-2	Relafen	Teva Pharmaceuticals Ltd.	[22]
			Indomethacin	Inhibition of prostagladins; Analgesic, anti-inflammatory and anti-pyretic	Indicid	John Lee Pharmaceuticals Pvt Ltd	[23]
			Prioxicam	COX-1 and COX-2 inhibitor	Feldene	Pfizer	[24]
		DMARDs	Leflunomide	Inihibits mitochondrial enzyme dihydro-orotate dehydrogenase	Lefno	Ipca	[25]
			Methotrexate	Inhibits aminoimidazole carboxamide ribonucleotide (AICAR) transformylase and thmidylate synthetase	Imutrex	Cipla	[26]
2.	Capsules	DMARDs	Sulfasalazine	Inihibits dihydrofolate reductase	Azulfidine	Pfizer	[27]
			Cyclosporine	Immunosuppressant; blocks the transcription of cytokines in activated T cells	Neoral	Novartis	[28]
			Minocycline	Binds to bacterial 30 s ribosomal subunit and inhibit preotein synthesis	Minoz OD	Ranbaxy	[29]
		NSAIDs	Indomethacin	Inhibition of prostagladins; Analgesic, anti-inflammatory and anti-pyretic	Donica	Ipca	[23]
3.	Liquid orals	DMARDs	Azathioprine	Immunosuppressant; inhibits *de novo* pathway of purine synthesis and therefore stops the DNA repilcation process	Imuran	Aspen	[30]
4.	Injectables	Biological DMARDs	Golimumab	TNF-α inhibitor	Simponi	Janssen Biotech, Inc	[31]
		DMARDs	Methotrexate	Inhibits AICAR transformylase and thmidylate synthetase	MEREX	Intas	[26]
5.	Topicals	NSAIDs	Diclofenac sodium	Inhibits prostaglandin and COX synthesis	Voveran	Novartis	[32]
			Ketoprofen		Fastum	A. Menarini Pharmaceuticals Ireland Ltd	[33]
		DMARDs	Methotrexate	Inhibits AICAR transformylase and thmidylate synthetase	Meth gel	West coast pharmaceuticals	[26]
6.	Transdermal patches	NSAIDs	Diclofenac sodium	Inhibits prostaglandin and COX synthesis	Voltarol, Nupatch	GSK, Zydus Cadila	[32]

and tetracyclines [50] are some common examples of DMARDs. Herbal agents too have been studied for ameleriotaring pain and inflammation caused due to RA, curcumin (CUR), capsaicin (CAP) and withanolides are some popular examples [51,52]. Most of these agents are administered systemically and lacks specificity to the organs/ tissues affected by RA resulting in extra-articular adverse effects [47]. Moreover, due to the short half-life and insufficient concentration of drug at the site of action, frequent dosing is required which results in patient incompliance. To overcome these limitations, there is a growing demand for development of novel drug delivery systems such as nanoemulsion, solid lipid nanoparticles, liposomes, ethosomes, niosomes and transferosomes [47].

Similar to tumor-targeted strategies, where nanoparticles exploit the enhanced permeability and retention (EPR) effect of solid tumours for increased accumulation at tumor site, nanoparticles can also be designed to extravasate from the highly permeable vasculature of RA affected regions and to be further sequestered by inflammatory cells. This phenomenon is termed as extravasation through leaky vasculature and subsequent inflammatory cell-mediated sequestration (ELVIS) effect [53,54]. Arthritic inflammation induces about 6- to 40-fold increase of blood joint barrier permeability [55]. An ideal drug delivery system for RA should be able to deliver the drug to the affected synovial joints. Oral drug delivery systems in this regard lack specificity and therefore result in serious side effects such as gastric bleeding, renal impairment and hepatic injury [56]. With continuous use of corticosteroids systemic side effects such as bone loss, peptic ulcers, buffalo hump, etc are observed [57]. These off target effects greatly decrease safety and patient compliance. To overcome these limitations, parenteral route of drug delivery has been extensively studied by researchers. Higaki et al. evaluated the therapeutic activity of IV administered PLGA nanoparticles encapsulating betamethasone sodium phosphate to produce slow release and targeted delivery [58]. PLGA nanoparticles encapsulating triptolide have been reported to produce anti-inflammatory effect in adjuvant induced arthritis in rats [59]. However, rapid systemic clearance of drug remains a matter of concern as it needs frequent drug administration [60]. Intra-articular administration of corticosteroids has also been proven to produce symptomatic relief in joint inflammation [61].

In recent years, topical route i.e. transdermal drug delivery has gained increased attention as it is non-invasive in nature and is patient compliant due to ease of application. Additionally, dermal route of drug delivery is also accompanied by advantages such as sustained action, dose flexibility, reduced side effects, ability to bypass hepatic first pass metabolism, and prevention of drug inactivation by gastroinetestinal pH and enzymes [62]. However, the low permeability of drugs through the stratum corneum stands as a bottleneck for wider applications of transdermal drug delivery route. The stratum corneum is the outermost layer of epidermis composed of dead keratinized cells called corneocytes surrounded by lipid layers. As a result, the stratum corneum is impermeable to water and behaves like tough flexible membrane which limits the diffusion of drugs. Researchers have experimented with various technologies to increase drug permeation, i.e iontophoresis [63], sonophoresis [64], microneedle [65] and electroporation [66], etc. In this regard, nanoformulations such as liposomes, nanoemulsions, niosomes, ethososmes, sold lipid nanoparticles have been used to overcome the problem associated with topical conventional formulation [67]. These formulations are generally incorporated into a gel base for better penetrability and to gain prolonged residence time for efficient reduction of RA induced inflammation [68].

This review discusses the novel approaches in drug delivery system including vesicular systems and lipophilic nanoparticulate carriers as shown in Fig. 3. The lipophilic carriers include solid lipid nanoparticles and nanoemulsions. On the other hand, the vesicular systems include liposomes, ethosomes and niosomes.

4. Lipophilic nanocarriers

4.1. Nanoemulsion

Nanoemulsions (NEs) are transparent, biphasic, isotropic and kinetically stable colloidal dispersions, with vesicular size of less than

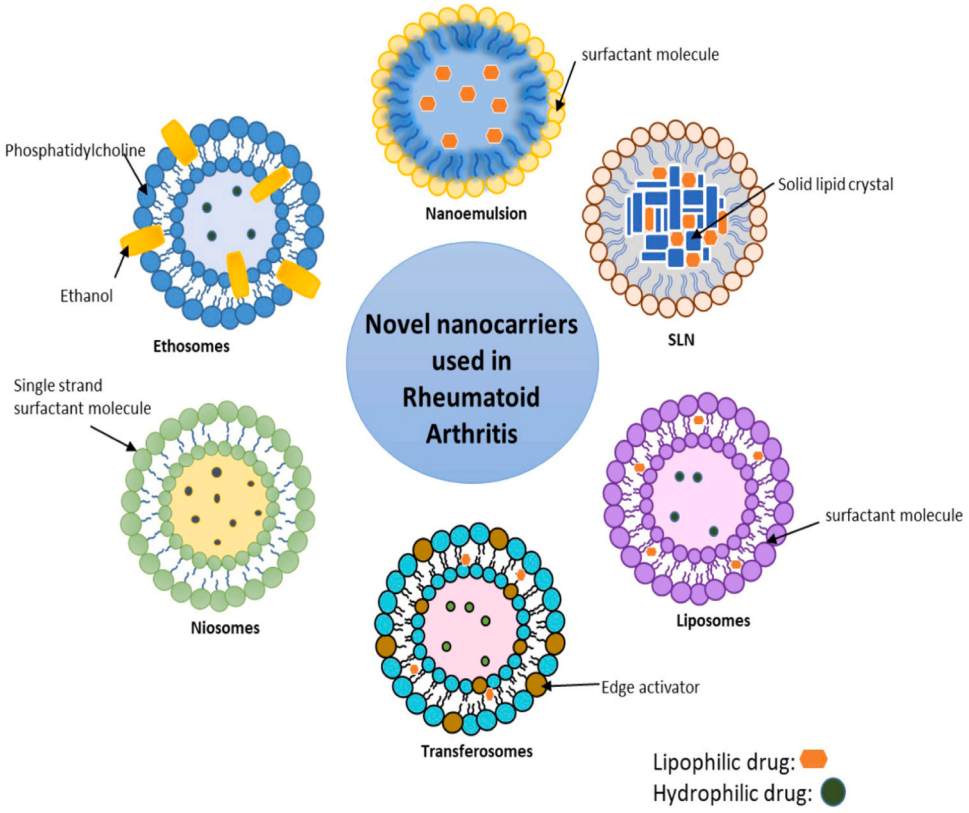

Fig. 3. Nanocarriers for management of Rheumatoid Arthritis.

200 nm. They are generally composed of emulsified oil, water and amphiphilic molecules [69,70]. NEs are used as drug delivery vectors especially for poorly soluble and poorly permeable drugs such as MLX, EXB, CLX to increase their solubility and drug loading, thereby ultimately improving the bioavailability of the drug [71]. Due to their small size, they easily penetrate through the rough surface of the skin, therefore enhancing the skin penetration of the drugs. This presents as a potential application to circumvent the chemical/enzymatic degradation of the drugs from the gut and the first-pass metabolism upon oral administration. Brownian motion dominates gravitational forces for NE due to their small droplet size, thereby favouring high kinetic stability towards flocculation, interface deformation, coalescence, etc [72]. However, NEs exhibit thermodynamic instability i.e., they cannot be formed spontaneously and instead requires external input energy [73]. NEs are formed by either high energy emulsification (High pressure homogenization, microfluidization and ultrasonication) or low energy emulsification (spontaneous emulsification and phase inversion technique) [74]. NEs are characterized by particle size, zeta potential, viscosity and electrical conductivity. Freeze fracture transmission electron microscopy is used to analyze particle size while polydispersity index determine the homogeneity of the dispersion. 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 [75].

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 [76]. 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 globule size of less than 200 nm. EXB-NE not only exhibited enhanced permeation through porcine abdominal skin, but also showed significant inhibition (84.61%) of edema in carrageenan-induced paw edema in rats as compared with conventional gel (69.23%) [77]. Shakeel et al. encapsulated IND within NE composed of Labrafil M1944CS (oil phase), tween 80 (surfactant), Transcutol-HP (co-surfactant) and water. The anti-inflammatory activity of IND loaded NE was compared in in-vivo rat model with commercially available Indobene gel, and was found to have superior and sustained anti-inflammatory activity over a period of 12 h. Although, the ingredients used in this study fall within generally regarded as safe (GRAS) category, skin irritation was observed as the concentration of surfactant and co-surfactant was increased from 33% and 11–45% and 15% respectively. Therefore, the safety of NE formulations with respect to each individual component is of paramount importance for safety, stability and efficient delivery of encapsulated drug [78].

The characteristics of NEs like size, viscocity and drug solubility can also be controlled by changing the NE composition. Lu et al. demonstrated size of NE to be critical factor in skin permeation. They observed that D-limonene NE with the smallest droplet size of 54 nm achieved maximum permeation rate through rat abdominal skin in Franz diffusion cell as compared to NEs with size range of 149–335 nm [79]. El-Leithy et al. increased the solubility of IND by 610-fold as compared with its solubility in water by varying the surfactant/cosurfactant type and concentration in the NE formulation. They observed NE containing pluronic surfactant to have the smallest globular size of 4–15 nm as compared to NEs with Tween 80 as surfactant (size >100 nm). This selective decrease in NE size with pluronic was attributed to its interaction with IND, which decreases the aggregation of pluronic molecules thereby decreasing the micelle size [80]. Similarly, Pathan et. al observed decrease in droplet size with increase in surfactant concentration (Polysorbate 80) for topical delivery of meloxicam (MLX) NE. This phenomenon was attributed to greater stabilization of oil droplets due to localization of surfactant at the oil-water interface [81]. In another study, Ilić et al., used sucrose esters (SEs) to stabilize NEs and

also act as skin penetration enhancer to improve delivery of Aceclofenac (ACF) into/across the skin barrier. *Ex vivo* permeation studies using porcine ear skin demonstrated nature of surfactant to largely affect the permeation of NEs. When compared with NE stabilized with ploysorbate 80, SE-NE demonstrated enhanced permeation of ACF and had the highest steady-state flux and permeation coefficient. The enhanced permeation of ACF-NEs in presence of SEs were attributed to destabilization of the densely packed lipids in the stratum coreum thus allowing least resistance for drug diffusion. The choice of gelling agents also affects the nature of emulgel in terms of colour, clarity, transparency, homogeneity, clogs, grittiness and consistency [82]. For instance, Chandra et al. experimented with various types of gels to incorporate ginger extract containing NE such as carbopol 934, HPMC K4 and tragacanth. They found Carbopol gel to be more transparent, clear and homogenous without any grittiness, while HPMC K4 and tragacanth gels were more turbid and cloudy in nature which discouraged their use to form an emulgel. The stability of the NE can also be assessed by percentage transmittance, which depends on particle size and distribution range (PDI). A monodispered oil-in-water (o/w) NE would have its percentage transmittance equal to aqueous phase transmittance due to uniform distribution of the oil droplets in water. The composition of oil in NE can affect the percentage transmittance of NE [83]. For instance, Nigam et al. formulated two different CAP loaded NE formulation, one consisted of oleic acid (10%) and another was formulated with labrasol as the oil phase. They observed NE containing labrasol had 99% transmittance while NE composed of oleic acid was turbid and lacked visual clarity [84]. Jeengar et al. used NEs to increase the permeation of curcumin (CUR), a poorly water soluble antiinflammatory drug with limited skin permeability. The NE composition consisted of emu oil, Cremophor RH 40 and Labrafil M2125CS as oil phase, surfactant and co-surfactant respectively. CUR loaded NE (CUR-NE) was later incorporated into a carbopol gel for convenient application by topical route. *Ex-vivo* studies showed significant improvement in penetration of CUR from NE as compared to CUR dispersion in oil and aqueous dispersions. These findings were also validated with in-vivo anti inflammatory studies on carrageenan induced rat paw edema model, where CUR-NE exhibited maximum inhibition of paw edema (66%) as compared with pure CUR gel (14.22%) [85]. In another similar study, Gokhale et al. optimized quercetin (QCT) loaded NE based gel to form a stable NE composed of oleic acid, arachis oil, tween 20 and PEG-400 (15:6:6) which acts as oil phase, permeation enhancer, surfactant and co-surfactant respectively. *Ex-vivo* permeation studies by using wistar rat abdominal skin showed enhanced permeation of 62% QCT from QCT-NE gel than from free QCT gel ie 35% at the end of 24 h. Further, in vivo studies in wistar rats also corroborated the superiority of NE loaded QCT with decreased paw circumference (50 mm) as compared to control group (71 mm) [86]. Pleguezuelos-Villa et al. incorporated biopolymer hyaluronic acid (HA) for stabilization of the NE formulation and also to increase the bioavailability of herbal antiinflammtory drug mangiferin. Along with increasing the residence time of the formulation on skin due to its mucadhesive nature, HA also possess tissue regeneration activities which are beneficial for inflamed RA tissues. *Ex-vivo* penetration studies pig skin showed highest penetration of mangiferin (2.5-fold) with NE containing low molecular weight HA. Moreover, in-vivo studies exhibited groups treated with mangiferin loaded HA-NE showed about 20 fold decrease in inflammation as compared to the control groups [87]. In another study, Ghiasi et al. compared the efficacy of CAP encapsulated NE in two different topical dosage forms ie Carbopol® gel and cream. CAP NE-gel showed the highest potential for inhibiting edema in carrageenan induced rat paw models. The better performance of CAP NE-gel over CAP NE-cream was theorized to be due to modification of nanodroplets in the cream base which otherwise remained intact during the gelification process by Carbopol®. Additionally, the hydrophilic matrix of Carbopol® gel was thought to be unable to retain capsaicin and the oil phase of NE as; both of which are hydrophobic in nature. While the hydrophobic property of the cream base prevented release of capsaicin or nanoemulsion thus inhibiting its therapeutic effect [88]. Hamed et al. formulated NE based gel of diclofenac diethylamine to evaluate its efficacy in treatment of RA as chronic oral administration of this drug leads to side effects. o/w nanoemulsion was incorporated in carbopol 971P. The release pattern of the gel was evaluated which showed a controlled release for 12 h following Korsemeyer Peppas model. Ibuprofen (IBF) is one of the most highly prescribed drugs but it is difficult to maintain effective concentrations in topical formulations due to its poor penetration property [89]. Salim et al. prepared IBF NEs by phase inversion composition method using oil:surfactant ratios (10:90, 20:80 and 30:70) and 80% of water to form a ternary system of palm kernel oil esters (PKOE)/Cremophor EL/ water. Droplet sizes below 50 nm with PDI below 0.2. Addition of the IBF to this NE, greatly reduced the droplet size and PDI. The cause of the decrease in the droplet size was attributed to the amphiphilic behaviour of the drug and its interaction with Cremophor EL. The drug permeation flux of IBF from PKOE and Miglyol 812 NE through human skin showed similar which suggest use of vegetable oil PKOE as an alternative to Miglyol 812 in developing NEs for topical delivery [90].

4.2. Solid lipid nanoparticles (SLNs)

In recent years, the lipid nanoparticles such as nanoemulsions, nanostructured lipid carriers and lipid-drug conjugates have attracted interest from the researchers in this field. In addition to these, nanoparticles with a solid lipid matrix i.e solid lipid nanoparticles (SLNs) have been developed with great potential in increasing cutaneous drug delivery of both hydrophilic and lipophilic drugs, compared to the other conventional vehicles [91,92]. SLNs are spherical colloidal systems with and average diameter in the range 40–1000 nm [93]. SLNs are composed of a lipid core with high melting point surrounded by surfactants. SLNs are also coated with hydrophilic polymers in some cases to improve its colloidal stability [94]. Lipids such as beeswax, stearic acid, cholesterol, glyceryl stearate (mono- and tri-), solid paraffin behenic acid, etc are used as solid lipid matrix [95]. Other ingredients such as surfactants, co-surfactant, preservative, cryoprotectant and charge modifiers are used for preparation of the SLNs. SLNs present several advantages such as high physical stability, negligible skin irritation, controlled release of drug, protection of the incorporated labile drugs against degradation and excellent in-vivo tolerability. SLNs are also used to increase the bioavailability of poorly soluble drugs and achieving targeted therapy by engineering a targeting ligand on the surface of SLNs [96]. When topically administered, SLNs demonstrate skin hydration properties and adhesiveness. A monolayer is formed on the skin after application, which offers occlusive properties and delays the loss of moisture from the skin. This reduces the corneocyte packing and opens intercorneocyte gaps resulting in penetration of drug into the deeper layers of skin [97]. The major techniques for formation of SLNs are high pressure homogenization (hot homogenization, cold homogenization), ultrasonication, solvent emulsification, microemulsion based, double emulsion technique and supercritical fluid based [98]. Studies indicate that small sized particles show higher barrier properties for evaporation and increase the occlusion. This effect of lipid nanoparticles is dependent on the applied volume, size of particle, and crystallinity of the lipid matrix [95,99]. The concentration of the lipid and surfactant plays an important role in the entrapment of the drug. Jain et al. studied the effect of surfactant: lipid ratio on particle sie and encapsulation efficiency of fluriprofen (FP) loaded SLNs. Stearic acid and cholesterol were selected as lipids while Pluronic F-68 was chosed as the surfactant. As the concentration of pluronic F-68 was increased from 0.4 to 1 of the total lipid content, an increase in average particle size (70–807 nm) was observed with subsequent decrease in FLP entrapment from 95% to 60%. Furthermore FP-SLN topical gel showed sustained release upto 5 h [100].

Properties like particle size, drug loading and release and stability are tightly controlled by their composition [101,102]. The composition

of the SLN lipid matrix not only influences its physiochemical properties like particle size, surface charge and drug entrapment efficiency, but also affects the drug release profile [103]. For instance, lipids with short-chain or complex triglycerides such as trimyristin, trilaurin and Witepsol H35 forms a supercooled melt after hot-melt homogenization, which results in uncontrolled release of drug [104]. On the other hand, waxes and pure triglycerides forms a highly crystalline structures that have poor drug encapsulation [105,106]. To overcome these issues, researchers have combined both short chain triglycerides and waxes such that a less ordered structure is formed and adequate drug encapsulation is achieved. Chantaburanan et al. studied the effect of such binary solid lipid matrix of wax (Cetyl palmitate (CP)) and triglyceride Softisan 378 (S-378) on lipid crystallinity and drug release of IBF loaded SLNs. They observed decrease in the particle size as the content of triglyceride S378 was increased, which was attributed to decrease in viscosity of the dispersed phase. The encapsulation efficiency of IBF in SLNs was found to be in an impressive range of 98.86–99.98%, suggesting complete entrapment of IBF within the SLNs. Drug release studies in phosphate buffer pH 5.5 exhibited a biphasic pattern with fast release initially followed by a sustained release. The initial fast release was attributed to the accumulation of IBF in the outer shell or at the interface of SLN. Moreover, as the concentration of triglyceride S378 was increased in the SLN matrix, a slower IBF release rate was observed, which was theorized to be due to localization of drug within the nanocompartments of liquid S378 dispersed throughout the solid matrix [107]. Another approach is to use excipients that contain a blend of lipids. For example lipids like Geleol, Compritol 888 ATO, tripamitin and Precirol ATO 5 are often used for preparation of SLNs as they contain a mixture of mono-, di- and triglycerides that form less perfect crystals with many imperfections offering enough space to accommodate the drugs. Verma et al. prepared PIR-SLNs composed of lipid tripamitin and surfactant polyvinyl alcohol. The optimized formulation exhibited a particle size of 435 nm and 85% drug entrapment [108] along with drug entrapment efficiency, the lipid composition also affects the particle size of SLNs. For instance, in the same study, they also observed that Compritol-SLNs to have the largest particle size (~1000 nm) followed by Precirol (~980 nm) then Geleol SLNs (~700 nm). Moreover, as the lipid content increased from 5% to 10%, a subsequent increase in particle size was observed which was thought to be due to increased lipid aggregation at high concentration [109]. On the contrary, Syed et al. observed that increasing the concentration of lipid (GMS) in azathioprine (AZA) loaded SLNs, resulted in decrease in the mean particle size. This opposite effect of GMS was attributed to its co-surfactant like properties which reduces the surface tension to favour formation of smaller SLNs. Moreover, an increase in entrapment efficiency of AZA was also observed due to increased concentration of mono-, di-, and triglycerides which also act as solubilizing agents for AZA. The viscocity of the medium also plays a role in SLN formation. As at high lipid concentrations, the increased viscosity of the medium causes faster solidification of the nanoparticles, therefore preventing diffusion of drug from the external phase of the medium during preparation [110]. Urbán-Morlán et al. compared the colloidal stability of cyclosporine- SLNs prepared using Compritol 888 ATO and Gelucire 44/14. The measurement of the zeta potential can be used to comment about the storage stability of colloidal dispersion of SLNs. Compritol-SLNs were observed to have low zeta potential (<30 mV), resulting in rapid destabilization and low dispersion stability when compared with Gelucire-SLNs. Stability in terms of cyclosporine content was also studied, which revealed that after three months of storage, the drug content from SLNs decreased prompting leaching of drug from the matrix. This phenomenon was explained by polymorphic transformation of lipid which reduces the space in the matrix causing the drug to come out [66].

The assessment of drug loaded SLNs in an in-vivo setting is essential to prove its therapaeutic efficacy. Bhalekar et al. prepared piperine (PIP) loaded SLNs with 78.71% entrapment efficiency. *In-vivo* studies indicated significant bone and joint erosion in untreated arthritic control group, while complete freund's adjuvant (CFA) induced arthritis rats exhibited reduction in paw volume. Moreover when compared with oral SLN formulation of piperine, topical PIP loaded SLN gel demonstrated greater reduction in paw volume. The difference in activity of PIP loaded oral and SLN gel formulation can be attributed to its relative biodistribution. With oral formulations, the drug undergoes systemic circulation, while topically administered drug is more concentrated at the applied region. This phenomenon of topical SLN gel was corroborated by *ex-vivo* studies using rat skin where percent localisation of PIP in skin was found to be 79.33% and the % retained on the skin surface was found to be 4.53% [111]. In another study, Bhalekar et al. tested the utility of chloroquine SLNs (CQ-SLNs) gel against CFA induced arthritic rat models. Radiographic and histopathological studies indicated lesser bone and cartilage disruption as compared to marketed CQ phosphate gel [112]. Mohammadi-Samani et al. compared PIR-SLNs with commercial piroxicam gel formulation and found increased skin permeation of the drug released form SLN gel than from simple PIR gel suggesting the capability of SLN gel as an efficient drug delivery carrier for treating RA [113].

Researchers have also used nanocarriers for dual delivery of drugs. The incorporation of dual drugs not only has increases the therapeutic effect but it also decreases the concentration of individual drugs, thereby decreasing the related side effects. In one such study, Vijaya et al. prepared SLNs for dual drug delivery of methotrexate and doxycycline, using lipid tristearin and surfactant Pluronic F-68. The entrapment efficiency of MTX and DOX in SLNs was found to be 65% and 79% respectively, with a particle size of 157 nm and potential of −9.6 mV. Moreover, i*n-vitro* drug release studies indicated sustained release of both drugs for up to two days. Therefore, SLNs can be considered an attractive choice not only for delivery of single drug but also for a combination of drugs to treat chronic inflammatory conditions such as RA [114]. Many studies indicate herbal plant extracts to have good anti-inflammatory activity in treating RA. However, their low solubility in formulations often posses as a bottleneck for their wide spread applications. Jeevana et al. formulated SLNs to enhance the solubility of herbal drug curcumin (CUR) for treating inflammation similar to that in RA. The content of CUR in the SLNs were measured to be in the range of 98.7–99.3% indicating negligible loss of CUR during formation of SLNs. *Ex-vivo* studies using goat skin indicated high cumulative drug release (76.93%) from SLN topical gel within 30 min of application on the skin membrane. Similar results were observed in in-vivo pharmacological assessment where X-ray radiographic analysis indicated hind paw deformities in untreated rats, while no deformities and significantly reduced swelling of paws was observed in rats treated with CUR-SLNs [115].

Table
Characteristic features of nanocarrier used in management of RA.

Type of system	Carrier	Characteristic features	Ref.
Lipophilic system	Nanoemulsion	• NEs are transparent, colloidal dispersion with diameters ranging from 10 to 200 nm. • Improves the solubility and bioavailabilites of hydrophobic (lipophilic) drugs. • NEs can be formulated in range of formulations such as sprays, foams, creams and gels.	[116, 117]
	Solid lipid nanoparticles (SLNs)	• SLNs are spherical in shape with diameter in the range of 50–1000 nm. • Phospholipids are an important constituent of SLNs. They are amphiphilic in nature due to	[118]

(*continued on next page*)

Table (*continued*)

Type of system	Carrier	Characteristic features	Ref.
		which it increases cutaneous absorption of lipophilic as well as hydrophilic drug. • SLNs have greater entrapment efficiency for lipophilic drugs as compared to liposomes due to the presences solid lipidic matrix. • APIs such as genes, proteins, plasmids, DNA and drugs can be enclosed in SLNs.	
Vesicular systems	Liposomes	• Liposomes are phospholipid vesicles consisting of one or more concentric lipid bilayers. • Hydrophobic molecules are entrapped into the bilayer membrane whereas hydrophilic molecules are entrapped in the aqueous center.	[119]
	Niosomes	• Niosomes are closed bilayer structure which is a result of self assembly of nonionic surfactants in aqueous media. • Cholestrol is the chief lipid component in niosomes. • Lipophilic as well as hydrophilic APIs can be loaded in these structures due to the amphilic nature of niosomes. • Niosomes enables delivery of drug at the target site in a sustained/controlled manner.	[120]
	Transferosomes	• Transferosomes are ultradeformable vesicles consisting of a lipid bilayer and an edge activator. • Phosphatidylcholine (C18) is the chief lipid component in transferosomes. As this lipid is abundantly found in the cell membrane, it is well tolerated by the human skin and decreases the risk of hypersensitive reactions. • Based on the lipophilicity of the drug, it can be encapsulated within the lipid bilayer or the core.	[121]
	Ethosomes	• Ethosomes are phospholipid based nanovesicles which contains a high content of ethanol (20–45%). • Ethanol acts as an efficient permeation enhancer and also imparts elasticity to the vesicles. • Due to the elastic nature, these vesicles can squeeze themselves easily through the pores smaller than their diameters.	

5. Vesicular systems

5.1. Liposomes

Liposomes were first introduced in 1965 by Alec Bangham and have been successfully translated into therapeutic applications [122]. Liposomes are bilayer phospholipid vesicles with an aqueous core. These lipids are routinely used pharmaceutical excipients and are generally biodegradable and non-toxic in nature [16]. Moreover as these phospholipids have similar lipidic composition to the skin, they also act as permeability enhancers to increase the percutaneous absorption of drugs when administered through topical route. The improved skin permeation of liposomes with cationic lipids is known as "Donnan exclusion effect" [123]. Liposomes also act as a reservoir in the stratum corneum layer for transport of drug through the skin in a sustained manner [124, 125]. Puglia et al. incorporated IND loaded liposomes in a gel base for topical administration. They observed that hydrogel containing IND-liposomes exhibited more sustained in-vivo antiinflammatory effect in erythema induced healthy human volunteers than free IND gel formulation. The sustained release of IND over a period of 6 h was attributed to formation of an IND reservoir in the stratum corneum layer [126]. Tatheer et al. compared prednisolone (PD) encapsulated liposomal gel with hydrogel containing free PD. Higher drug entrapment and prolonged drug release was achieveable with PD liposomal gel. Another characteristic of lipsoomes is its versatility to incorporate both hydrophilic and hydrophobic drugs within the liposomal core and the lipid bilayer repesctively [127].

Liposomes are formed spontaneously when a phospholipid layer is disrupted by external force such as sonication or stirring or when it encounters an aqueous phase. The techniques involved in preparation of liposomal system are film hydration, reverse phase evaporation, injection method and freeze drying method [128]. Lipid composition, size, and surface charge affect the skin permeation of liposomes [129]. The lipid composition of liposome also affects the drug encapsulation and drug release profile. Begum et al. investigated the effect of cholesterol on the liposomal encapsulation efficiency of Celecoxib (CXB), a poorly water soluble NSAID. Their results demonstrated that liposomes containing optimum amount of cholesterol (12 mg), had excellent CXB encapsulation efficiency beyond which, a decrease in encapsulation as well as drug release was observed [130]. Based on their size and lamellarity, liposomes are classified as unilamellar vesicles (ULV), multilamellar vesicles (MLV), large unilamellar vesicles (LUV), and small unilamellar vesicles (SUV) [131,132]. However, the therapeutic applications of conventional unilamellar or multilammelar liposomes are limited due to their low entrapment efficiency as well as stability problems i.e. burst release of drugs due to unanticipated membrane breach. To overcome these challenges, researchers have designed multivesicular liposomes (MVL), which have multiple nonconcentric aqueous chambers surrounded by a network of lipoidal membranes [133]. These systems differ from ULVs and MLVs in terms of size and composition. ULVs and MLVs have a size range of 1–5 μm as compared to MVL's size range of 5–30 μm, which offer more space for drug encapsulation. Additionally, along with commonly used lipids for liposomes, MVLs also contain neutral lipid such as triolein, tricaprylin, tributyrin, and tributyrine that stabilize the membrane boundaries of the unique multivesicular structure [134]. The multiple acqueous vesicular structures allows for higher encapsulation of hydrophilic drugs. For instance, Jain et al. prepared MVL loaded with CXB- β-cyclodextrin complex. The rationale to compex CXB with β-cyclodextrin (β–CD) was to increase the hydrophilicity of CXB which in turn would favour its encapsulation in the numerous acqueous vesicles of MVL. Their results demonstrated superior CXB encapsulation of 88% in MVLs as compared to 27% CXB encapsulation seen in conventional liposomes. Drug release studies resulted in slow release of CXB i.e. 72% over a period of 24 h, which was explained by presence of multiple diffusion barriers. The slow drug release relected in sustaiend in-vivo anti-inflamatory activity where a 40% reduction in paw volume was observed even after 24 h in a carrageenan-induced rat paw edema model [134]. The superiority of lipososmal DEX over free DEX was corroborated in vivo by greater reduction of paw swelling. Proliposomes are novel carrier mediated drug delivery system having advantages over the conventional liposomes like better stability, ease of sterilization, prevention of drug over loading [135]. Kurakula et al. investigated the use of proliposomes as a delivery system using PD as an anti-inflammatory agent. Proliposome enclosing PD was prepared using thin film hydration. Proliposomes were formulated by optimizing the concentration of lecithin, cholesterol and mannitol. Proliposomal gels were formulated in 0.5, 1 & 2% w/w

concentration. The percentage yield of proliposomes and entrapment efficiency were reported to increase with increase in the concentration of phospholipid. *In-vitro* drug release was studied over dialysis membrane. PD proliposomal gels showed 50–80% release in 14 h as compared to 90% release from free drug gel in 14 h. *In-vivo* anti-inflammatory study in rats showed 60% inhibition as compared to 50% of diclofenac gel. Proliposomes exhibit superior stability when compared to traditional liposomes, thereby increasing its potential application in transdermal delivery systems [136].

5.2. Niosomes

In recent years, vesicular structures such as liposomes have gained increased attention for drug delivery applications. However inspite of their multifunctional characteristics, liposomes too have some drawbacks such as high cost of formulation, lack of stability at various pHs and limited shelf life due to the rancidification of lipids [137,138] To overcome these disadvantages, researchers have replaced the phospholipid content of liposomes with nonionic surfactants and cholesterol to form a nonionic surfactant vesicular system called as niosome [139]. Compared with lipsoomes, niosomes offer better chemical stability, longer shelf life, cost effective due to inexpensive nonionic surfactant and enhanced skin penetration of drugs which increases drug delivery to treat RA. Studies demonstrate that when administered through topical route, niosomes enhance the residence time of drugs in the stratum corneum and epidermal layer thereby improving the penetration of the drug across the skin [140]. They are theorized to decrease the transepidermal water loss and replenish lost skin lipids from the horny layer, which smoothenes the horny layer to facilitate easy drug penetration [138]. Additionally, when compared with vesicles containing anionic, cationic and amphoteric surfactants, niosomes do not cause hemolysis or irritation to cellular surfaces as they do not contain any charged surfactants. Most commonly used examples of nonioinic surfactants include alkyl ethers and alkyl glyceryl ethers, sorbitan fatty acid esters such as span 60, poloxethyelene fatty acid esters such as tween 20,40, 60 and so on. Moreover, the amphiphilic bi-layered structure of niosomes enables encapsulation of both hydrophilic as well as hydrophobic drugs by bonding with polar and non-polar sites within the membrane, respectively [141]. Similar to liposomes, niosomes can be structurally categorized as unilamellar, oligolamellar or multilamellar. The general techniques to form niosomes are also similar to that of liposomes, which include lipid film hydration, multiple membrane extrusion, micorfluidization, ethanol and ether injection method [142].

Several variables like type of non-ionic surfactant, method of preparation, temperature of hydration, etc, govern the formation and morphology of niosomes [143]. Ravalika et al. used two different methods ie thin film hydration and ether injection technique, for synthesizing niosomes for encapsulating etorcoxib. Their results demonstrated that nisoomes formed using thin film hydration technique had higher entrapment efficiency (about 96%) than those formed using ether injection method (93%) [144]. The particle size of niosomes are dependent on the repulsive forces between the bilayers and entrapped drug. Entrapment efficiency depends on the method of preparation, type of drug and surfactants [145,146]. Asthana et al. co-related the effect of cholesterol concentration with the particles size and entrapment effeciency of niosomes. They encapsulated etodolac (ETD) in niosomes containing various ratios of span 60 and cholesterol. Their results demonstrated that at low cholesterol concentration, smaller particles size niosomes were formed while further increasing the cholestr content, increased the particle size of the niosomes. This size difference was attributed to increased hydrophobicity of the bilayer membrane at high cholesterol concentration which leads to formation of large vesicles in order to attain a more thermodynamically stable form. Additionally, increasing the cholesterol content (0.5–1) also increased ETD entrapment efficiency up to 95%. However, further increase in cholesterol ratio from 1 to 1.5 decreased the entrapment efficiency, which was thought to be due to insufficient room available for ETD as cholesterol competes with ETD for packing space within the bilayer [144]. The concentration of cholesterol also affects the release of drug from niosomes. For instance, El-Menshawe et al. observed that niosomes containing high cholesterol concentration decreased the release of meloxicam (MX) from the vesicles which could be due to the increased cholesterol induced rigidity of the bilayer membrane [144]. Fathalla et al. studied the effect of various type and concentration of surfactant on the size of the noisome. They observed that nisosomes containing span 60 as the surfactant had larger particle size (15 μm) compared with those prepared with span 20 (size 1 μm). The vast difference in particle size inspite of using same surfactant class was attributed to the chemical structural difference between span 20 and span 60. Span 60 has a longer saturated alkyl chain (C16) compared to span 20 (C10) which results in larger vesicles due to increased hydrophobicity of the surfactant. On the other hand, an inverse relationship was observed between concentration of surfactant and vesicular diameter, which was attributed to decrease in free surface energy with increase in surfactant hydrophobicity [144].

The viscosity of the gel formulation also affects the release and penetration of the drug, as it may reduce the diffusion rate of the drug fro the noisome. Fathalla et al. evaluated different gel bases such as carbopol 934, sodium alginate, sodium carboxymethyl cellulose (NaCMC), hydroxypropylmethyl cellulose (HPMC) and pluronic F-127 for incorporation of niosomes containing ACE. Amongst these, HPMC was found to have the lease viscosity (6800 cp) and was selected as the gel base [140]. In addition to transdermal gel, researchers have also incorporate niosomes into transdermal patches for better applicability and longer adherence. For instance, Rajaram et al. incorporated PIR loaded niosomal gel in a transdermal patch comprising of PVP, Eudragit L 100 and EC polymer. The drug release kinetics was evaluated to be of zero-order along with non-fickian diffusion [147]. Another approach to weaken the skin barrier is addition of permeation enhancers. Manosroi et al. used ethanol in the formation of niosomes containing diclofenac diethylammonium (DCFD). Ethanol acts as an efficient permeation enhancer by decreasing the melting point of stratum corneum lipids, thereby increasing the lipid fluidity, and skin permeability. Moreover, presence of ethanol in the niosomes permits high elasticity enabling them to squeeze through the pores of the dermal layer. Transdermal absorption studies using rat skin corroborated these theories as the gel containing elastic niosomes exhibited high fluxes of about 3.76 microg/(cm^2 h) of DCFD in the franz receiver chamber as compared with commercial gel (0.14 microg/(cm^2 h)) containing an equivalent DCFD [148].

Alsarra prepared PIR loaded niosomes to evaluate its efficacy for anti-inflammatory activity. Various non-ionic surfactants were used to formulate an optimum niosomal formulation evaluating the permeation flux. The idea of formulating niosomes was based on the concept that the mixture of surfactant: alcohol: aqueous phase will form a concentrated proniosomal gel which with the addition of excess aqueous phase can then spontaneously for niosomal dispersion. The proniosomes were prepared using different non-ionic surfactants like Span 20, Span 60, Span 80 and Tween 80 which evaluated for its flux. It was observed that pro niosomes prepared using span 60 showed a higher release rate as compared to niosomes prepared using Span 20 and Span 80. Tween 80 showed a higher release rate as compared to niosomes prepared using the varied types of Span. This was attributed to the freely soluble characteristic of Tween as compare to the Spans. Span 60 showed the highest phase transition temperature which contributed to the highest entrapment efficiency of 91.7 ± 2% and a particle size of 4.81 ± 1.1 μm. This study could concluded that niosomes enhance the permeability of PIR2 by modifying the stratum corneum as the phospholipids and non-ionic surfactants act as penetration enhancers [149].

5.3. Transferosomes

Transferosomes are another upcoming vesicular nanoparticles for

drug delivery through dermal route. It is a proprietary drug delivery technology registered by the German company IDEA AG. Transferosomes have close resemblance to liposomes and are frequently referred as ultra-deformable lipids, ultra-flexible liposomes or as elastic liposomes. Structurally, tranferosomes is similar to liposomes in containing at least one inner aqueous compartment surrounded by a lipid bilayer. However, along with bilayer lipids, transferosomes also contain (10–25%) specialized surfactants known as edge activators which attributes to its elastic nature. Most routinely used edge activators are surfactants such as sodium cholate, sodium deoxycholate, span 80 and tween 80 [150]. These edge activators are usually single chained surfactants or non-ionic surfactants, which have the ability to destabilize the lipid bilayer and to reduce the interfacial tension, thus allowing the vesicles to deform with minimum energy in response to external mechanical stress. The concentration of edge activators govern the elasticity of the vesicles to enhance its dermal penetration, thus allowing these vesicles to shrink through the dermal barrier and along the transcutaneous gradient before reforming back to its original diameter [151–153]. This mechanism allows transferosomes to penetrate the dermal layers by either intracellular lipid or transcellular route. Like conventional liposomes, transferosomes have the ability to encapsulate small, moderate and highly hydrophobic well as hydrophilic drugs [154]. In this regard, transferosomes have been used for delivery of numerous therapeutic molecules such as anti-cancer drugs, corticosteroids and also nonsteroidal anti-inflammatory drugs used for treatment of RA [155–160]. In 2007, a transferosome formulation encapsulating KET has also received marketing approval by the Swiss regulatory agency (Swiss Medic).

Transferosomes are generally formulated using two techniques i.e. rotary evaporation followed by sonication method and vortexing-sonication method [161,162]. In the former method, phosphatidylcholine and edge activators are dissolved in an organic solvent which is later evaporated to form a thin film. The film is hydrated with drug solution and allowed to swell followed by sonication to form vesicles, as done in formation of liposomes. While in vortexing technique, phosphatidylcholine, edge activators and drug are mixed in phosphate buffer solution and vortexed to form a milky suspension followed by sonication. The concentration of lipid, edge activators i.e. surfactants, organic phase as well as hydration medium play a major role in moderating the size of the vesicles [163]. Dudhipala et al. studied the effect of type of edge activator on transferosomes loaded with **ACE**. Soylecittin and egg lecithin were selected as the lipids, while Tween 80, Span 80, sodium deoxy cholate, and sodium cholate as edge activators. Based on physical appearances, transferosomes formed using soylecittin exhibited better properties. Highest flexibility was demonstrated with Tween 80 and highest encapsulation efficiency was observed in transferosomes with Span 80. As sodium deoxy cholate and sodium cholate have steroid like bulky structure, the vesicles formed had less flexibility when compared with hydrocarbon chains of Tween 80. Sana et al. formulated transferosomes for encapsulation of CUR-TF, which were then embedded into carbopol-934 gel for topical application. They observed CUR-TF gel to have superior in vitro skin penetration than plain CUR, while in vivo studies in rat arthritic model also corroborated the improved therapeutic efficacy of CUR-TF by histological, x-ray scores and decreased levels of pro-inflammatory cytokines [164]. In another study, Simoes et al. demonstrated prophylactic use of drug laden transferosomes to suppress the induced rat paw edema [165]. Sarwa et al. formulated transferosomes using phosphatidylcholine and tween 80 for delivery of anti-rheumatic drug capsaicin. When compare with marketed Thermagel formulation at the same dose, CAP loaded transferosomes demonstrated better penetration and therapeutic ability in in vivo arthritic rat models [166]. Although transferosomes seem like an ideal choice for topical drug delivery, especially for treatment of RA, some of its limitations are; their susceptibility for oxidative degradation, re-organization of phospholipids and high cost of manufacturing [166].

5.4. Ethosomes

Although liposomes and niosomes offer great encapsulation and solubility of drugs, their application is limited as they are unable to penetrate deep into skin owing to their less flexible nature. Ethosomes are lipidic vesicles, similar to liposomes and niosomes but with higher concentration of ethanol (~10–50%), hence termed as "etho-somes" [167]. The high ethanol content enables these vesicles to be elasticity which aids in efficient penetration of ethosomes through the narrow channels in the skin and also by increasing the fluidity of skin lipids [168,169]. These "soft vesicles'' therefore present as novel vesicular carriers for enhanced delivery to/ through the dermal route. Moreover, the combination of alcohol and lipid vesicular system also results in enhanced entrapment of drugs [170]. Various methods have been employed to formulate ethosomes such as hot method, cold method and classic mechanical dispersion method [171,172].

Fan et al. formulated ethosomes and lipsomes containing herbal drug tetradrine for symptomatic treatment of RA. On comparing tetrandrine loaded ethosomes and liposomes, ethosomes were fairly smaller in size (78 nm) as compared with liposomes, which were of size 99 nm. The high ethanol content were presumed to modify the net charge of the system and also confer some degree of steric stabilization that led to a decrease in vesicualar size of ethosomes. Permeation studies using franz vertical diffusion cell and rat skin indicated higher transdermal flux and 2.1-fold higher delivery of tetrandrine from ethosomes through the stratum corneum barrier than their liposomal counterpart. *In-vivo* studies further corroborated the superior anti-athritic activity of ethosomes as significant in rat paw edema was seen in ethosome treated group as compared to liposomal treated group [173]. Moreover, in terms of stability, Sakdiset et al. observed ethosomes exhibite higher stability than liposomes as lipid aggregation was observed in liposomes within one week of formulation. The reason for aggregation was thought to be due to electrostatic and bonding interactions between the phosphatidylcholine of SPC in liposomes, which are otherwise discouraged in ethosomes. A remarkable decrease in vesicular size of IND loaded ethosomes at 20% ethanol concentration. However, at 30% ethanlic concentration the vesicular size increased, which was attributed to organization of lipids in the vesicular membrane [174]. Abdelbary et al. aimed to improve the transdermal delivery of mometasone furoate (MF) via ethosomal system. The skin flux of ethosomal system was 2.33 and 3.53 folds as compared to liposomal system and hydroalcoholic solution respectively. Comparative in-vivo study among conventional MF gel, ethosomal gel and marketed formulation in CIA model revealed that daily application of ethosomal gel for 21 days showed complete a complete recovery of tibiofemoral joint [175]. In another study, Sarwar et al. observed superior permeation of ethosomal CAP vesicles with a flux of 15 cm/h $\times$ 10^{-3} in modified diffusion cell at the end of 24 h, which was higher than the commercial CAP product ie Thermagel and also the hydroethanolic solution of CAP. Confocal laser scanning micrography further confirmed passing of capsaicin-loaded vesicles throughout the epidermal barrier. Similar results were obtained in CFA induced arthritis rats where CAP-loaded ethosomes significantly inhibited paw edema by 40% as compared with 15% inhibition by Thermagel [176].

Another vesicular system similar to that of ethosomes are transfereosomes which contain edge activators (surfactants) along with lipids, which drastically reduce the value of its elastic module ie make it more elastic in nature [177]. A hybrid structure of ethosomes and transfersoemes would significantly increase skin permeation. In one such attempt, Garg et al. combined the properties of both transfereosmes and ethosomes to formulate PIR loaded transethosomes with Span 80 as edge activator. They evaluated the flexibility of PIR loaded transethosomes in terms of deformability index and elasticity using membrane extrusion method. Their results demonstrated transethosomes to pass easily through a pore size that was 12.73 times smaller than that of their size. Thus demonstrating higher elasticity than liposomes and even

ethosomes to pass easily through the dermal layer. This effect was also validated through *ex vivo* permeation studies, where the transethosomal formulation exhibited the highest drug permeation through porcine skin as compared to other gel formulations [178]. Researchers have devised various approaches to further narrow down the release and effect of drugs, such as attaching targeting ligand, designing stimuli responsive delivery system and so on. In RA, reactive oxygen species (ROS) are abundantly formed at inflamed site which can be targeted by drug delivery systems. In one such study, Song et al. decorated the surface of sinomenine hydrochloride (SIN-HCl) loaded transethosmes with antioxidant ascorbic acid to increase its localization at inflammatory sites via redox interaction in the presence of a high level of ROS. The transdermal permeability efficiency of these transethosomes was 98% higher than that of ethosomes [179]. Chourasia et al. evaluated the potential of ethosomes for enhanced topical delivery of Ketoprofen (KET). KET is an anti-inflammatory agent with poor transdermal permeability despite attempts to improve it permeability through topical gels and patches. In this study, Chourasia entrapped KET in the lipidic bilayer of phosphotidylcholine with enclosed ethanolic core. Ethosomes with particle size range of 362.5–406.3 nm was observed at 2.5–3% SPC and 20–25% ethanol content. Entrapment efficiency was found to increase to 73% with higher concentration of ethanol due to enhanced solubility of the drug in ethanol. An increase in the amount of SPC retarded the drug release whereas an increase in the amount of ethanol increased the drug release. 81.4 ± 5% drug release was observed in the 24 h study. The increase in the release due to higher amount of alcohol was observed because of increased amount of fluidity of the bilayer membrane. The permeation profile of the ethosomal formulation was compared with hydroethanolic solution of the drug. The highest transdermal flux was observed in ethosomal formulation containing 1% SPC and 40% ethanol as obtained from the surface plot. Decrease in the amount of ethanol with same concentration of SPC resulted in the lowest transdermal plot. The enhanced permeability was contributed by the alcohol content which interacts with lipids in the stratum corneum by increasing its fluidity. After the penetration, the drug release depends upon the interaction of the formulation along with the skin lipids [180]. To investigate the transdermal delivery potential of diclofenac potassium, a water soluble drug, Vijayakumar used ethosomes as a vesicular carrier and performed a comparative study between ethosomal, liposomal formulation. Diclofenac potassium is completely absorbed from GIT and undergoes extensive first pass metabolism in the liver. Oral dose of diclofenac potassium causes severe gastrointestinal adverse events including ulceration, bleeding which could be fatal. To overcome these effects and enhance the efficacy, transdermal delivery was explored for diclofenac potassium. Formulation consisted of phosphotidylcholine and ethanol and drug was fixed at 1% w/w and was made by mechanical dispersion technique. The entrapment efficiency from different formulations ranged from 18.74% to 72.91%, highest efficiency was obtained with 4%w/v SPC and 40%v/v ethanol. The effect on vesicular size of the ethosomes was observed to decrease with increased ethanol concentration and increase with increased phospholipid concentration. Increase in the contents of ethanol and phospholipid caused increase in entrapment efficiency. The cumulative drug release from ethosomal formulation was found to be 60.37%, comparatively higher than 15.95% from the liposomal formulation. Skin permeation reports showed 4 times enhanced permeation than liposomes. Carbopol 980 was used a gelling agent. *In vivo* anti-inflammatory effect was measured as % inhibition. Ethosomal gel showed 44.44% inhibition as compared to 35.80% of marketed after 4 h of application. This study exhibits the potential of ethosomes as a carrier for diclofenac potassium with improved permeation and anti-inflammatory effect [181].

6. Clinical trials conducted for treatment of Rheumatoid Arthritis

Conventional DMARDs and biological DMARDs may fail, or produce unwanted side effects or give partial effect, thereby new antirheumatic drugs are being developed and are undergoing clinical trials at various sites to study their efficacy for the treatment and management of RA symptoms and further study the side effects if any as compared to the conventional therapy. [182]. There are number of drug molecules, biologics or combination therapies which have shown promising results during various clinical trail conducted by various agencies across the globe. Clinical trials are conducted in accordance to the official guidelines for clinical research of respective countries. This guidelines mainly addresses the dose-selection, efficacy assessment, safety of the drug and drug product [183]. Table 2 summarizes various clinical trials conducted in US, Canada, Europe and India for the development of anti-rheumatic drugs, preparation methods and combination targets.

7. Patents filed for treatment of Rheumatoid Arthritis

The global data reports suggests that the burden of RA is expected to increase between 2015 and 2025 in eight major markets (8MM) i.e. US, France, Germany, UK, Spain, Italy, Brazil, Australia and Japan. The epidemiologists forecast an hike in total number of cases from 6,137,523 in 2015 to 6,971,304 cases in 2025, with annual growth rate of 1.36%. In 2015, US accounted for 45.90% of prevalent cases of RA in the 8MM. The development of newer therapies and molecules has resulted in a large number of clinical trials as mentioned above and there is increase in patent applications filled in the USA and other major countries of 8MM. Patents related to RA was primarily sourced from google patents database using search strings such as rheumatoid arthritis, topical treatment, nanoformulation, etc. The resulting information was classified according to countries in which the patents were granted namely US, India, Canada, Japan, Australia, European Nation, etc. Country specific website such https://www.ic.gc.ca/opic-cipo/cpd/eng/search/basic.html for Canada and http://pericles.ipaustralia.gov.au/ols/auspat/quickSearch.do for Australia were also used for patent search. Table 3 discusses about the various patents granted in different countries for treatment/management of RA.

8. Conclusion and future prospectives

Treatment of rheumatoid arthritis involve chronic use of drugs such as NSAIDs, corticosteroids, DMARDs, biologics, that might lead to gastric irritation, impaired wound healing, osteoporosis, peptic ulcers. liver and kidney dysfunctions, suppressed the immune response. To overcome the side effects and elevate the efficiency of drugs, treatment needs to be site specific. The search of the novel topical delivery systems have resulted in development of nanocarriers that can effectively penetrate the layer of skin when administered through topical route. These nanocarriers promise specific and local delivery of drugs to the targeted inflamed joint. Moreover, they also reduce the quantity of drug used, thus decreasing the potential of unwanted off-target effects. Patients within high-risk populations can also consider using these nanocarrier based delivery systems.

Lipophilic nanocarriers and vesicular systems show great potential for selective drug delivery to inflamed barriers. Lipophilic nanocarriers such as nanoemulsions and solid lipid nanocarriers improve the solubility of poorly water soluble drugs, thereby improves the drug loading, confers stability and helps in dose reduction. Liposomes are versatile in terms of composition, surface modification and encapsulation of variety of drugs. However, since most of it is composed of lipids, they are most suscesptible to undergo degradation via lipid oxidation. Niosome is a good alternative to lipsomes, as it is composed of surfactants which are far more stable than that of lipids. Like liposomes, niosomes to have favorable drug delivery features such as high drug loading efficiency, versatile payload capability and sustained release of drug. However, it is crucial to monitor the type of surfactants and its toxicological limits. Transfersomes are structurally similar to liposomes, but contains special surfactants on the edge where makes them elastic and ultradeformable.

Table 2
Clinical trials for treatment of RA.

Country	Identifier	Study title	Phase	Sponsor/Collaborator	Status
United States	NCT04559412	Study to assess the safety and efficacy of Enbrel administered by Sofusa DoseConnect for Rheumatoid Arthritis	I	Sorrento Therapeutics, Inc.	Recruiting
	NCT04464642	Tofacitinib Versus Methotrexate as the first line DMARD in the treatment of rheumatoid arthritis	IV	Bangabandhu Sheikh Mujib Medical University	Active, not recruiting
	NCT04535427	Role of L-arginine supplementation in the treatment of rheumatoid arthritis	II	RenJi Hospital	Not yet recruiting
	NCT02675803	Safety, tolerability, pharmacokinetics and pharmacodynamics study of VAY736 in rheumatoid arthritis patients	I	Novartis Pharmaceuticals	Completed
	NCT03368235	Early phase study to assess efficacy and safety of AZD9567 versus prednisolone in patients with rheumatoid arthritis	II	AstraZeneca	Completed
	NCT01948388	The effect of corticotrophin (ACTH) in combination with methotrexate in newly diagnosed rheumatoid arthritis patients	IV	Gaylis, Norman B., M.D.	Completed
	NCT02167139	A study comparing SB5 to Humira® in subjects with moderate to severe rheumatoid arthritis despite methotrexate therapy	III	Samsung Bioepis Co., Ltd.	Completed
Canada	20120262	A randomized, double-blind, phase 3 study of ABP 501 efficacy and safety compared with adalimumab in subjects with moderate to severe rheumatoid arthritis	III	Amgen	Ongoing
	IM006016	Phase 2, randomized, multi-center, double-blind, dose-ranging, placebo controlled, adaptive design study to evaluate the efficacy and safety/ pharmacokinetics of BMS986142 in subjects with moderate to severe rheumatoid arthritis with an inadequate response to methotrexate with or without tnf inhibitors.	II	BRISTOL-MYERS SQUIBB CANADA	Closed
	202018	A 24-week, phase 3, multicentre, randomised, double-blind, efficacy and safety study, comparing GSK3196165 with placebo and with sarilumab, in combination with conventional synthetic DMARDS, in participants with moderately to severely active rheumatoid arthiritis who have an inadequate response to biological DMARDS and/or janus kinase inhibitors	III	GLAXOSMITHKLINE INC	Ongoing
	ML30171	A randomized, double-blind, placebo-controlled, phase 2 study of safety, tolerability and efficacy of pirfenidone in patients with rheumatoid arthritis interstitial lung disease	II	BRIGHAM AND WOMENS HOSPITAL	Ongoing
	CNTO148ART3003	A golimumab phase 3B, multicenter, assessment of intravenous efficacy in rheumatoid arthritis subjects who have diminished disease control despite treatment with infliximab (remicade)	III-b	JANSSEN INC	Ongoing
Europe	2010–023469–22	A phase II study of ARA 290 as therapeutic strategy in rheumatoid arthritis	II	LUMC	Ongoing
	2011–005634–19	A Phase 2b Study to Evaluate the Efficacy and Safety of Mavrilimumab in Subjects with Moderate-to-Severe Rheumatoid Arthritis.	II-b	MedImmune Ltd	Completed
	2011–002392–41	A phase II, double-blind, controlled, multi-center, randomized, long term safety trial of Z102 and prednisone (5 mg or 7.5 mg) in patients with moderate to severe rheumatoid arthritis	II	Zalicus, Inc.	Completed
	2010–022207–22	A Phase 3, Multicenter, Randomized, Double Blind, Placebo Controlled Study to Evaluate the Efficacy and Safety of LY2127399 in Patients with Moderate to Severe Rheumatoid Arthritis (RA) who had an Inadequate Response to one or more TNF-α Inhibitors (FLEX-V)	III	Eli Lilly and Company	Completed
India	CTRI/2020/04/ 024644	A Non-interventional, observational Post Marketing Surveillance (PMS) Study of AdaliRelTM (Adalimumab) in Patients With Active Rheumatoid arthritis.)	IV	Reliance Life Sciences Pv Ltd	Not Yet Recruiting
	CTRI/2020/03/ 024153	A clinical study on Meganathi kuligai for UthiraVatha suronitham (Rheumatoid Arthritis)	III	Cipla Ltd R and D Centre	Completed
	CTRI/2009/091/ 000402	A Clinical Trial to study the Safety, Tolerability and Effect of Tocilizumab in Patients with Active Rheumatoid Arthritis taking Background Non-biologic DMARDs and having an Inadequate Response to Current Non-biologic DMARD and/or Anti-TNF Therapy	II	Government siddha medical college and hospital	Not Yet Recruiting
	CTRI/2021/02/ 031361	Comparing two different ways of giving oral methotrexate (a first line drug) in rheumatoid arthritis - to look at difference in benefit and side effects when giving it as a single dose versus as a split dose (some dose in morning and some in evening)	IV	Postgraduate Institute Of Medical Education And Research Chandigarh	Open to Recruitment
	CTRI/2020/11/ 029047	Curcumin for the Management of Periodontitis and Early Rheumatoid Arthritis: Killing Two Birds with One Stone	N/A	Dr Manjunath S M	Not Yet Recruiting
	CTRI/2020/09/ 027958	This multi-center, randomized, double-blind research study will be conducted to understand the effectiveness and side effects of drug Golimumab (R-TPR-044 / Simponi®) in patients with active Rheumatoid Arthritis (pain and swelling in joints) on a stable dose of methotrexate.	III	Reliance Life Sciences Pvt Ltd	Open to Recruitment

Hence, tranfersomes can highly improve the dermal penetration of poorly water soluble drug molecules. Ethosomes containing ethanol as the membrane barrier can be used as a safer alternative. Despite, studies indicating high stability of these vesicular structures, a rupture in the membrane can result in premature release of drug, resulting in off-target effects. Solid lipid nanoparticles in this regard offer better stability than its vesicular counterparts. Several researchers have demonstrated the ability of all these carriers to improve skin permeation and/or to achieve cutaneous targeting of a large variety of active ingredients, depending on both vehicle composition and active ingredient physical-chemical properties. In order to the address the issue of penetration and absorption of various drug across the skin layer, pharmaceutical industry have adopted various approaches such as penetration enhancement via modification of the stratum corneum by hydration, use of chemical

Table 3
Patents granted in the field of RA.

Identifier	Title	Claims	Active compound	Current Assignee	Patent granted
CA2778441C	Hydrated microparticles of apigenin and/or luteolin with improved solubility	Flavonoids such as apigenin and luteolin exhibit anti-inflammatory properties. The solubility of flavonoid is less than 1 mg/ml or less than 0.1 mg/ml. Incorporation of apigenin and/or luteolin in hydrated nicroparticles can improve the solubility in water.	Apigenin	Vizuri Health Sciences LLC	2019–01–08
US10058519B2	Treatment of pain with topical diclofenac	Effect of 1.5% Diclofenac sodium solution was study for six weeks effective for treatment of the pain and symptoms of knee osteoarthritis when applied QID to the knee.	Diclofenac	Hznp Medicines LLC	2018–08–28
EP2265125B1	Topical LFA-1 antagonists for use in localized treatment of immune related disorders	Topical administration of LFA-1 antagonist in form of ester or any other acceptable salt form was found to be beneficial in treatment of inflammatory or immune related disorders.	Heterocyclic compounds	Sarcode Bioscience Inc	2019–08–14
CA2669918C	Topical formulation comprising Comfrey and Tannic acid, and uses thereof	Comfrey root/leaf and tannic acid is used in treatment of osteoarthritis and rheumatoid arthritis. Amount of comfrey or comfrey-derived compound in the topical formulation can be altered in the range of 0.5–40% of the total weight of the topical formulation to suit a particular use. Amount of tannic acid in the topical formulation can be altered in the range of 2–20% of the total weight of the topical formulation to suit a particular use.	Comfrey and tannic acid	Arthritis Relief Plus Ltd	2020–03–10
CA2760460 Al	Pharmaceutical compositions for the treatment of inflammatory disorders	Cyclopropanecarboxylic acid salts were found to be useful in the prophylaxis and/or treatment of various inflammatory conditions, autoimmune diseases, proliferative diseases transplant rejection, allergies, etc.	Cyclopropanecarboxylic acid derivative	Galapagos NV AbbVie Deutschland GmbH and Co KG	2019–12–03
CA2760460C	Transdermal formulations of cannabidiol comprising a penetration enhancer and methods of using the same	A pharmaceutical composition containing 0.1–20% cannabidiol would provide analgesia, reduce inflammation, help alleviate nausea and emesis, etc.	Cannabidiol	Zynerba Pharmaceuticals Inc	2019–04–02
CA2820625C	3-methanesulfonylpropionitrile for treating inflammation and pain	The purified 3-methanesulfonylpropionitrile and salts were found to treat inflammation and related diseases.	3-methanesulfonylpropionitrile	Olatec Therapeutics LLC	2019–04–02
CA2875619C	Aminotriazolopyridine for use in the treatment of inflammation, and pharmaceutical compositions thereof	An acceptable salt form of aminotriazolopyridine was used to treat inflammatory conditions, autoimmune diseases, allergies,etc.	Aminotriazolopyridine	Galapagos NV	2020–11–24
CA2680413C	Use of gelsolin to diagnose and treat rheumatoid arthritis	The use of plasma gelsolin was found to be beneficial for preventing as well as treating RA.	Gelsolin	Brigham and Womens Hospital Inc	2020–06–09
AU2014314053B2	Antibodies neutralizing GM-CSF for use in the treatment of rheumatoid arthritis or as analgesics	The invention relates to neutralizing antibodies of GM-CSF and treating inflammatory disorders such as RA and pain associated to it.	Antibodies	Takeda GmbH	2020–03–12
AU2014352801B2	Compositions for the treatment of rheumatoid arthritis and methods of using same	The invention provides method and composition of treating the symptoms of RA using specific antibody that binds to human IL-6 receptor.	Anti-IL-6R antibodies	Sanofi Biotechnology SAS Regeneron Pharmaceuticals Inc	2020–05–28

enhancers, nanocarriers and solubility effects. The ability of the chemical penetration enhancers such as isopropyl myristate, oleyl alcohol, propylene glycol, triacetin, etc to accelerate stratum corneum permeation through the skin barrier is dependent on the physico-chemical properties (e.g. melting point, molecular weight, molecular geometry, charge, lipophilicity, etc.) of the drug. For new drugs detailed study must be conducted in order to determine the optimal choice of penetration enhancer and/or formulation to achieve desired dermal delivery. By changing The molecular properties and/or choose of an appropriate delivery system (permeation enhancer or nanocarrier) can lead to optimal penetration through a desired pathway. An understanding of the various possible routes for skin penetration can help in selection of an appropriate system that will deliver the molecule to the desired site of action. The combinatorial approach of permeation enhancers and nanocarriers has the potential for effective permeation enhancement at lower active concentrations than separate approaches. Overcoming the skin barrier in a safe and effective way either by chemical, physical or by vesicular nanotechnology based approaches, still remains a major challenge for topical applications. As there is progress in understanding the properties and the actual potential of these delivery systems, new pharmaceutical and cosmetic products based on these colloidal nanocarriers can be considered as potential treatment formulations for management of rheumatoid arthritis. Newer and more versatile nanocarriers such as nanoparticles, nanogels, nanostructured lipid carriers, cubosomes, exosomes self nano and micro-emulsifying drug delivery systems, etc are also explored in management of RA. However, to discuss these nanoformulations at length is outside the scope of this article.

In the near future, newer DMARDs and biologicals DMARDs are

likely to be developed for treatment of RA and other chronic inflammatory diseases. These nanoformulations have potential to move towards clinics trails due to the ability to reduce drug dose, dosing frequency and side effects. Progression of RA along with new dosage regimen with nanoformulations may significantly improve the quality of a RA patient.

CRediT authorship contribution statement

I, **Munira Momin**, the corresponding author of this manuscript, certify that the contributors and conflicts of interest statement included in this paper are correct and have been approved by all co-authors. All the authors have contributed equally in this paper. Furthermore, each author certifies that this material or similar material has not been and will not be submitted to or published to any other publications.

Conflict of interest statement

The authors declare that there are no conflicts of interest. All co-authors have seen and agree with the contents of the manuscript and there is no financial interest to report.

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