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Review Article

NANO-STRUCTURED LIPID CARRIERS: A PROMISING STRATEGY AND CURRENT PROGRESS IN RHEUMATOID ARTHRITIS AND PAIN MANAGEMENT

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Abstract

Rheumatoid arthritis is among the predominant holistic and persistent joint-related autoimmune diseases that causes in physical impairment and impaired quality of functioning, since bone & cartilage degradation, joint inflammation, as well as pain arise. Despite significant innovations in treatment strategies, restrictions on treatment routes and A requirement for a regular, long-term dosage have manifested in clinical unpleasant effects and patient rebellion that could have been controlled through producing nano-structured lipid carriers (NLCs) based systems. Pain is another prevalent and growing global medical challenge which has enormous economic and social impact to both patients and medical-care services, and therefore on the society overall. NLCs offer a fascinating opportunity as innovative strategies to pick up safety and effectiveness of the medications widely used for pain relief. In this article, we reviewed the benefits and drawbacks, classification, components used and manufacturing techniques, i.e. the methodology of heat and cold homogenization for NLCs. A summary was also elucidated of the types and pathogenesis of rheumatoid arthritis. Here we explore a wide range of NLC formulations produced to encapsulate a variety of medication to treat rheumatoid arthritis as well as pain illnesses, their compositions and methodologies of preparation.

***Keywords*:** Rheumatoid arthritis; Nano-structured lipid carriers; Pain management; Homogenization technique.

Introduction

Rheumatoid arthritis (RA) is prevalent multidisciplinary as well as chronic joint-related autoimmune disorders that results in physical disability and compromised standards of living, because deterioration of cartilage and bone, pain and swelling of joints take place. Recent advancements along with new strategies for cure have dramatically prevented the advancement of illness and boosted the living conditions for several patients. With major breakthroughs in medication alternatives, constraints on the routes of medication regular dosing for longer periods manifested in systemic side effects as well as individual's non-compliance that might be managed by developing systems based on nano-structured lipid carriers (NLCs) (Dolati *et al*., 2016). Pain is yet another pervasive and rising medical problem globally that has a tremendous social and financial influence on both individuals and healthcare systems, and hence on community itself. Although existing medication regimens provide a broad spectrum of pharmacological/non-pharmacological alternatives, such interventions are not necessarily successful in minimizing and relieving pain based on the severity of the problem and individual variations in medical responses. However, several pain management medications like non-steroidal anti-inflammatory drugs (NSAIDs), opioids and local anesthetics show several harmful side effects. Recent trends in science in this therapeutic domain are also focused on the discovery of new therapies to solve many of the unaddressed challenges and to resolve the current shortcomings of treatment. As innovative tools, NLCs offer an interesting potential to increase the effectiveness and safety of drugs commonly used for pain management (Andreu *et al*., 2018). NLCs are colloidal particles of a size range of 50-1000 nm consisting of a mixture of solid and liquid lipids which remain solid at room as well as body temperature and demonstrate increased drug loading and less drug leakage during storage compared to solid lipid nano-particles (Figure 1) (Ganesan and Narayanasamy, 2017; Huang *et al*., 2008; Mehnert and Mäder, 2012).

In this review, we discussed about advantages and disadvantages, classification, materials used and production methodology *i.e.* hot and cold homogenization technique for NLCs. An overview of types and pathogenesis of rheumatoid arthritis has also been elucidated. Herein, we discuss about broad variety of NLC formulations which have been produced to encapsulate a range of drugs used for treatment of rheumatoid arthritis and pain conditions, their compositions and preparation methods.

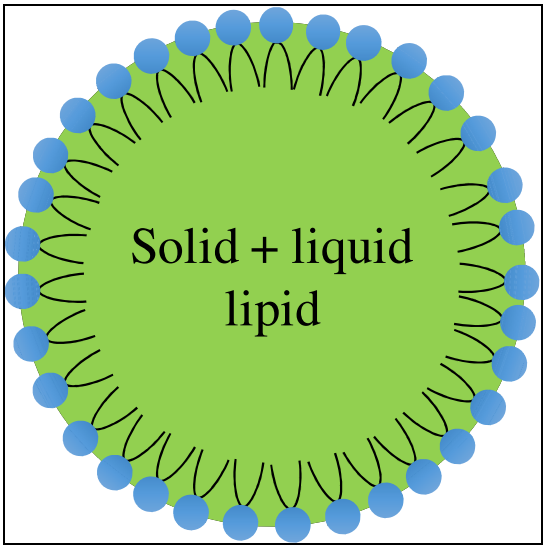


Fig. 1 : Nano-structured lipid carrier

Advantages and disadvantages of NLCs

NLCs have several advantages which makes this an excellent drug delivery system for RA and pain therapy (Figure 2) (Lauterbach *et al.,* 2015; Nunes *et al.,* 2017; Sánchez-López *et al.,* 2017; Wissing *et al.,* 2004). Few drawbacks of NLC as drug delivery system includes high water content in lipid dispersion, gelation of lipid dispersion, and initial burst drug release may induce toxic effects (Beloqui *et al.,* 2014*;* Tran *et al.,* 2014*;* Xiang *et al.,* 2007).

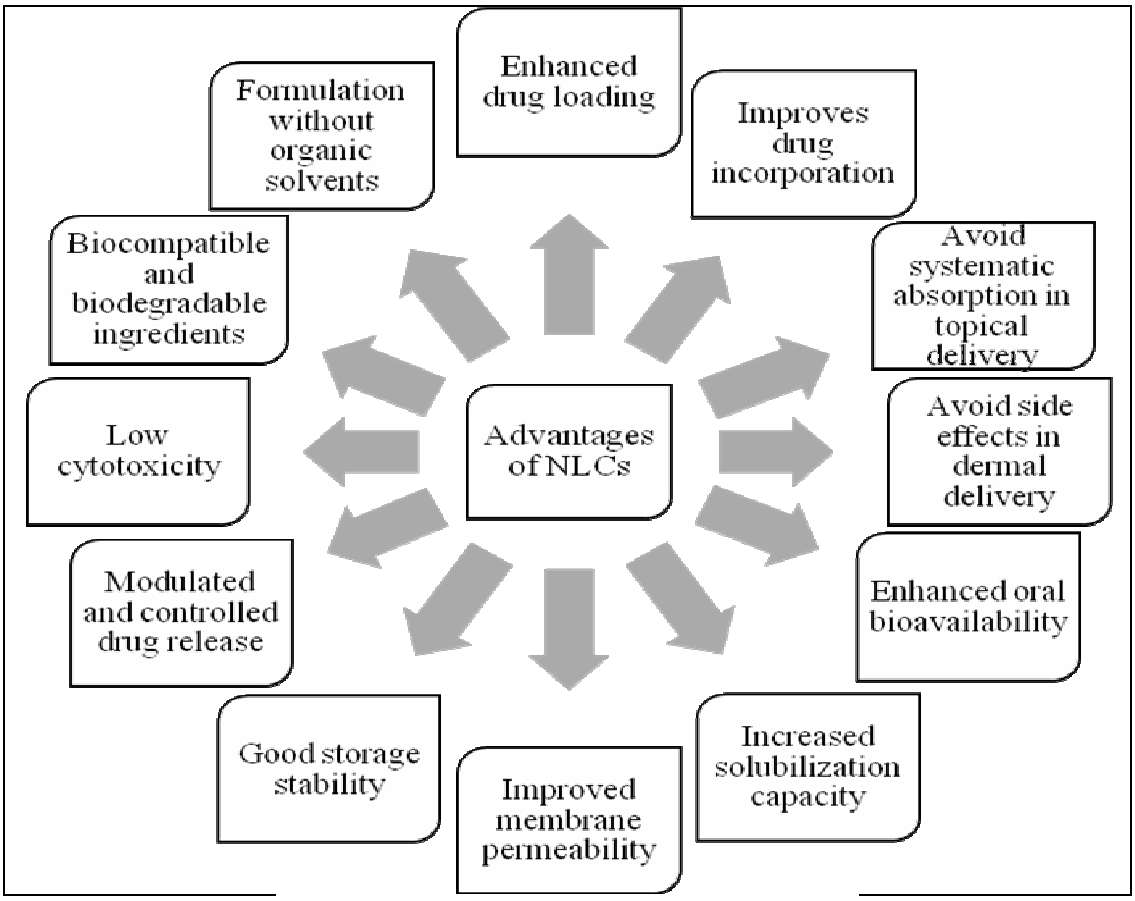


Fig. 2 : Advantages of NLC as drug delivery system

Classification of NLC

The various types of NLCs include imperfect crystal, amorphous crystal and multiple emulsions (Figure 3) (Jenning *et al.,* 2000; Muller *et al.,* 2002).

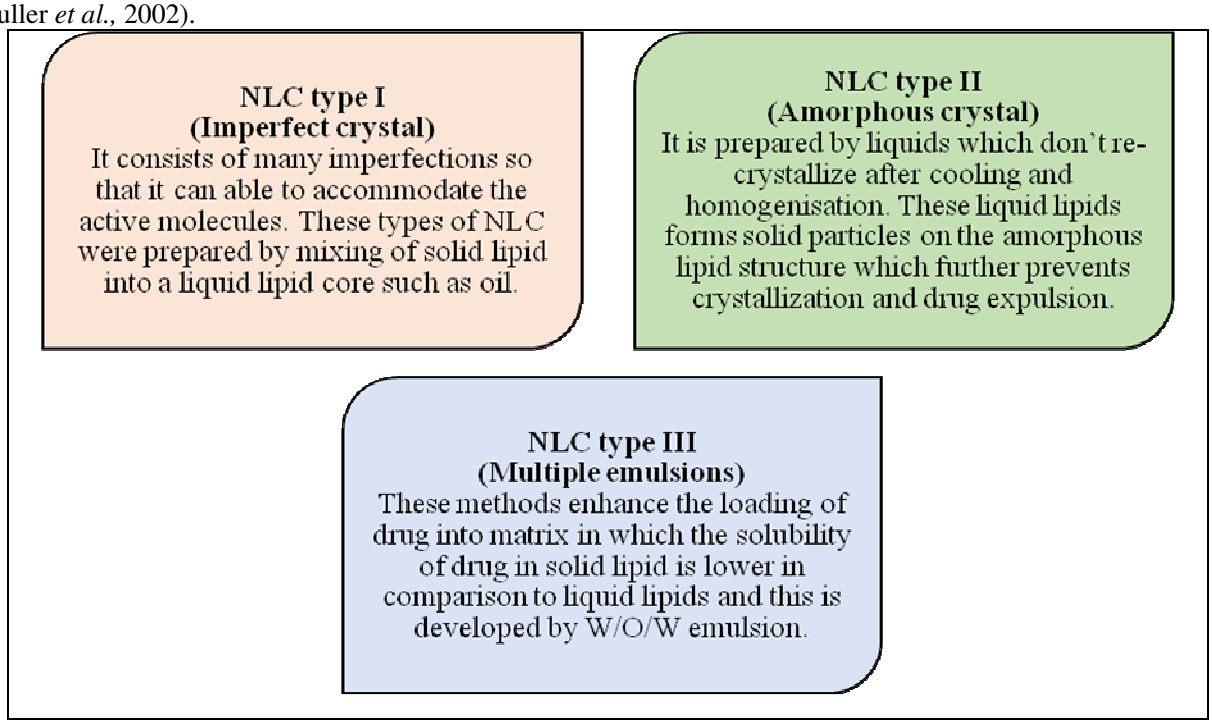


Fig. 3 : Classification of NLCs

Materials used for the synthesis of NLCs

Phase	Materials
Liquid lipid	2-Octyl dodecanol, Transcutol HP, Labrafil Lipofile WL 1349, Labrafac PG, Medium chain triglycerides, Paraffin oil,
Solid lipid	Dynasan116, Cetyl palmitate, Cutina, Cholesterol, Precirol ATO 5, Dynasan 118, Softisan 154, Tristearin, Stearic acid
Amphillic emulsifier	Egg lecithin, Soya lecithin, Phosphatidylcholines
Lipophyllic emulsifier	Span 20, Span 40 and Span 60
Hydrophyllic emulsifier	Poloxamer 188, Poloxamer 407, Tween 20, Tween 80, Tween 40, Polyvinyl alcohol, Solutol HS15, Sodium deoxycholate,

Method of preparation of NLCs

A variety of both chemical and physical methods for the synthesis of NLCs have been established. These methods provide significant advantages such as low energy requirements, easily applicable and feasible and high potential yield. The classification of production techniques of NLCs are summarized in Figure 4 (Ganesan and Narayanasamy, 2017).

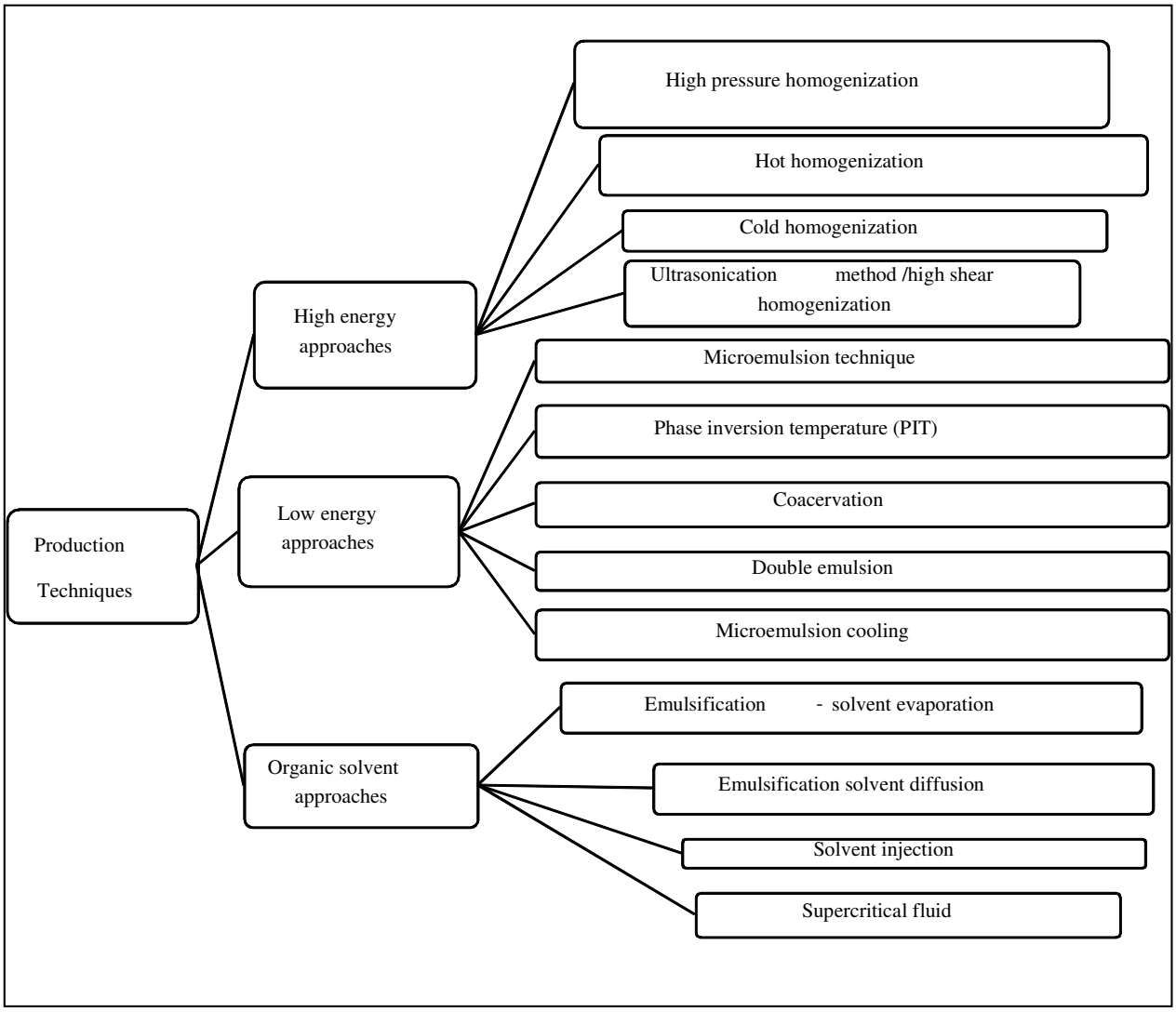


Fig. 4 : Production techniques for nano-structured lipid carrier

Hot homogenization technique is most preferred which includes the melting of the lipid, followed by addition of drug and surfactant. Pre-emulsion is formulated using a homogenizer which is cooled at room temperature and re-crystallized to produce NLCs. This method is advantageous as it is scalable and commercially available but shows certain limitations such as thermal deterioration of the drug, the difficulty of nano-emulsion crystallization stage led to many alterations and super-cooled melts (Figure 5) (Bunjes *et al*., 1996; Lim and Kim, 2002). Cold homogenization technique overcomes the limitations of hot homogenization. This method is similar to hot homogenization as the drug is dispersed in hot lipid solution and mixed properly. The drug lipid solution is cooled with liquid nitrogen or dry ice. Fine powder of solid is obtained by milling into micro-particle. Obtained microparticles are immersed into a surfactant solution which will formed NLCs by dispersing it into high pressure homogenization. This method is advantageous as it prevents the temperature induced degradation (Figure 6) (Ganesan and Narayanasamy, 2017; Jaiswal *et al*., 2016; Mehnert and Mäder, 2001).

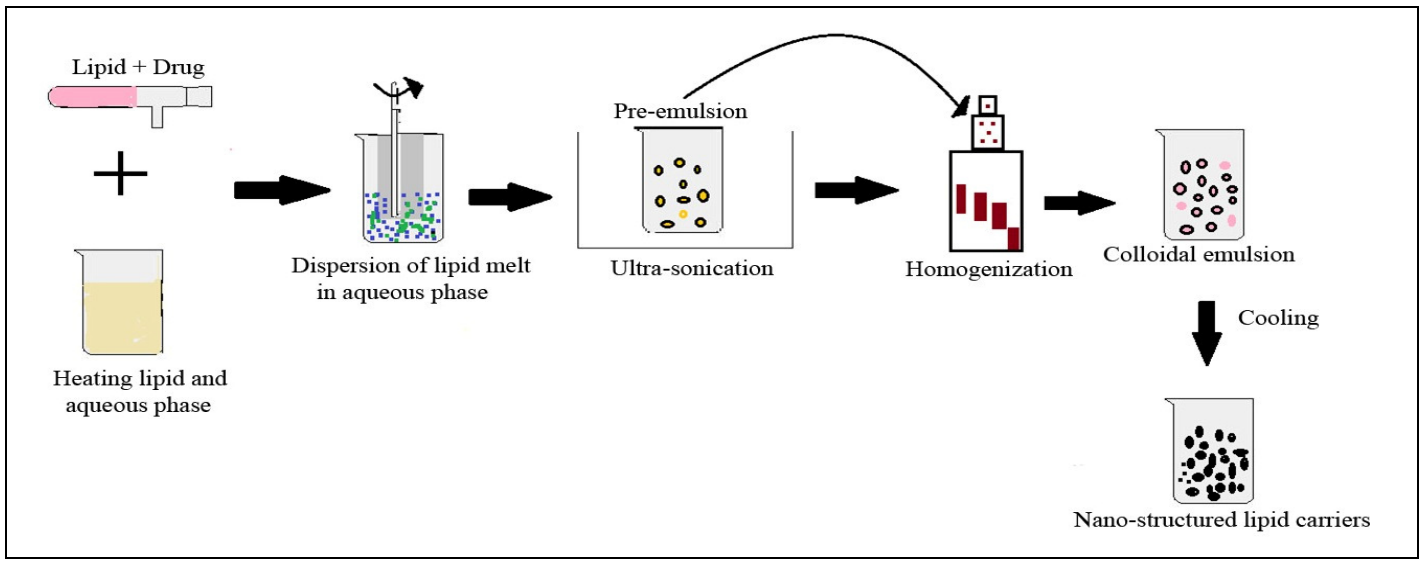


Fig. 5 : Hot homogenization technique

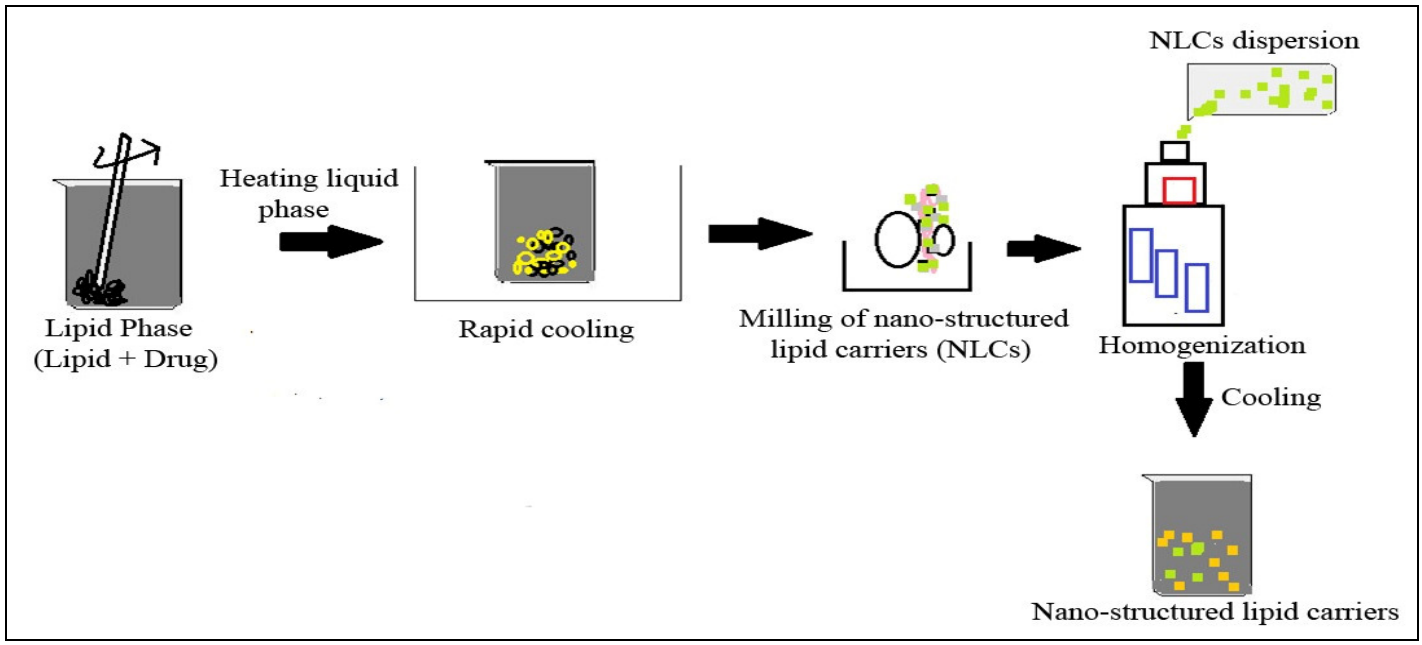


Fig. 6 : Cold homogenization technique

Types and pathogenesis of Rheumatoid Arthritis

Various types of rheumatoid arthritis have been depicted in Figure 7 (Braun *et al.*, 2007; Fantini *et al.*, 2003; Martin *et al.*, 2002; Ogdie *et al.*, 2015).

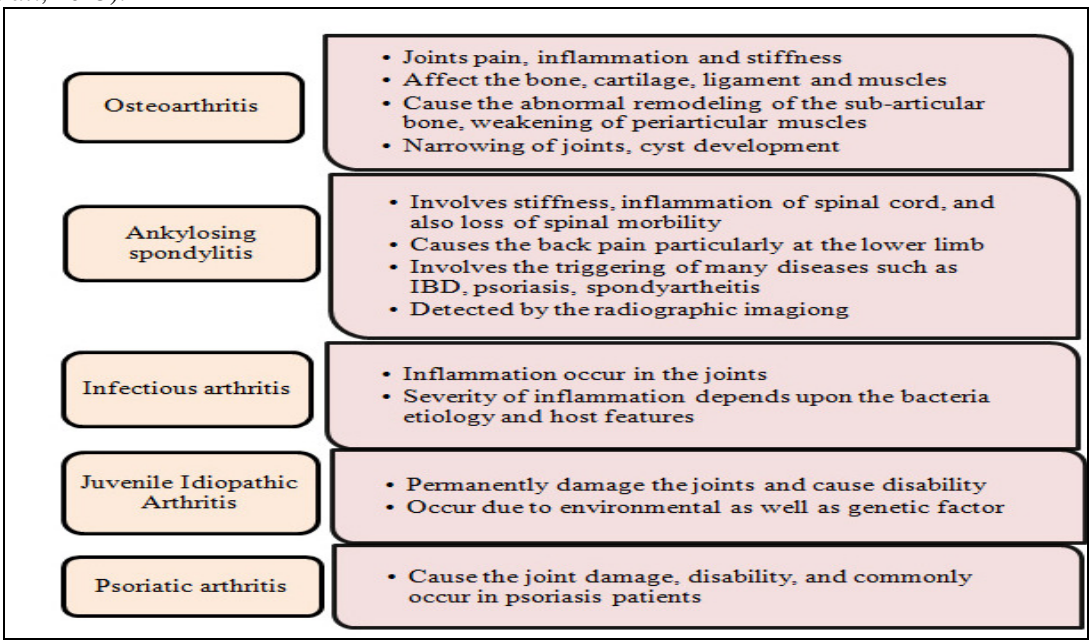
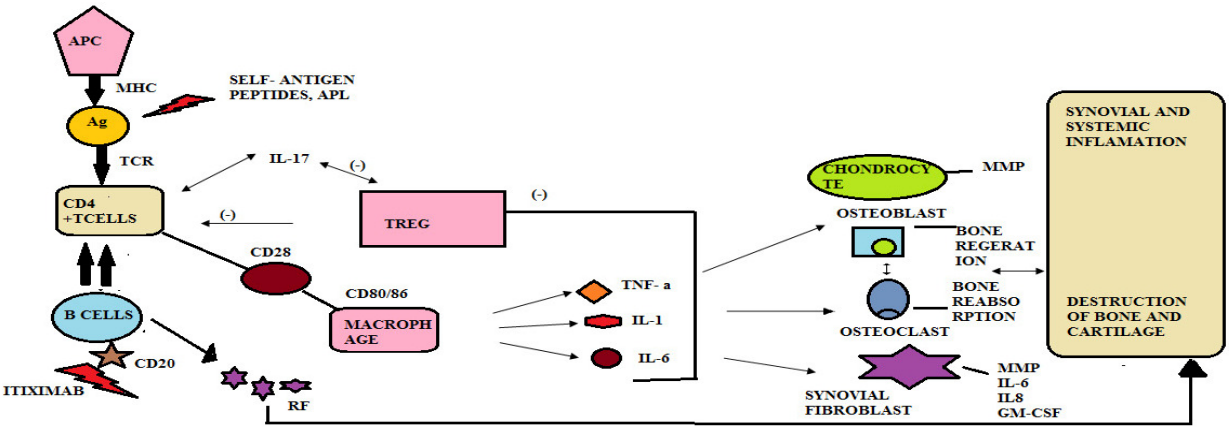


Fig. 7 : Types of arthritis

The chronic inflammation of the joint that arises through rheumatoid arthritis is caused by stimulated T-cells that attack synovial membrane. The recognition through CD4 + T-cells of such a hypothetical antigen, accompanied with the activation of specific cytokines, activates the differentiation of certain lymphocytes into phenotypes Th1 and Th17. The pathophysiology of RA has been illustrated in Figure 8 (Barberá *et al*., 2012; Boissier *et al*., 2008; Gaffen, 2009; Hoffmann *et al*., 2009).



Ag: Antigens; APC: Antigen-presenting cell; APL: Altered peptide ligand; RF: Rheumatoid factor;
GM-CSF: Granulocyte-macrophage colony; MHC: Major histocompatibility complex; MMP: Metalloproteases;
TCR: T-cell receptor; TNF-α: Tumor necrosis factor-alpha;
Treg: Regulatory T-cell; (-) sign indicates a negative or suppressive effect on pro-inflammatory cytokines or on certain cell groups.

Fig. 8 : Pathophysiology of rheumatoid arthritis

Application of NLCs in Rheumatoid Arthritis

Garg *et al* synthesized methotrexate (MTX) filled NLCs and chemical enhancer (CE) co-incorporated hydrogel (gel-(MTX-NLCs+CE) using lipid phase (stearic acid, gelucire, transcutol P), utilizing hot microemulsion technique. Arthritis index, paw and ankle bones arthritis ranking, and histopathology were assessed and concluded that formulated hydrogel demonstrated greater therapeutic activity than free medication (Garg *et al*., 2016). Another group of researcher explored Flurbiprofen loaded NLC and after storage of 3 months at 4, 20 and 40ºC flubiprofen loaded NLC showed little difference in zeta potential, particle size, and ph value. After 12 h of storage, FP loaded NLC demonstrated an improved *in-vitro* release rate of the drug (412.53±21.37 µg/cm) while FP loaded PBS at 7.4 pH release rate was 90.83±8.67 µg/cm. It was concluded that finally prepared FP loaded NLC displayed improved release rate, entrapment efficiency of FP compared with other FP formulation for trans-dermal delivery (Han *et al.,* 2008). In a study, cell-penetrating peptide-coated tripterine-loaded NLCs were developed by solvent evaporation techniques to enhance oral bioavailability of tripterine. *In- vivo* and *in- vitro* drug release was determined using rat perfusion model and dialysis bag diffusion technique, and concluded that prepared CT-NLC displayed lower intestinal cytotoxicity, higher absorption in rat duodenum. CT-NLC was observed to have a particle size, encapsulation capacity and zeta potential of 126.7±9.2 nm, 72.64±1.37 percent, and 28.7±3.4 mV. The pharmacokinetic analysis revealed that the CT-NLC prepared revealed optimum concentration, concentration ads time compared with tripterine solution and suspension (Chen *et al.,* 2012a). Zhao and his colleague's explored ability to control pentapeptide mounted NLCs on *in-vitro* and *in-vivo* macrophages and showed increased anti-inflammatory activity with this drug delivery system. Size of Pen-NLCs and bare-NLCs were 203.0±8.5 nm and 190.0±1.0 respectively. (Zhao *et al*., 2013). In another study, Diflunisal phospholipid complex was encumbered into a supra-molecular nano-engineered lipid carriers (SNLCs) for trans-dermal delivery using solvent- evaporation technique using L8 taguchi orthogonal array design and particle size (188.1 nm), skin retention (17.72 ± 0.68 µg/cm2), entrapment efficiency (86.77 ± 3.33%), permeation flux (5.47 ± 0.48 µg/cm2/h) was determined. In rheumatoid arthritis, SNLC showed diminish synovial fluid in TNFα (146.74±1.69 mg/mL) and serum (132.43±2.70 pg/mL) and hang-up of paw edema was widely elevated (73.85±14.5%) (Kaur *et al*., 2017). In this research, Dexamethasone is loaded into an NLC using lipid process to resolve low water solubility using emulsification-ultrasound technique and DA-NLC (7.6 µg/ml) has showed better anti-inflammatory action than free drug (0.9 µg/ml) and may be a prospective carrier to augment beneficial effectiveness on inflammation (Xu *et al*., 2011). Nirbhavane *et al.* synthesized celecoxib (CXB) primed SLN gel using phospholipon 90G (lipid phase) for the treatment of rheumatoid arthritis using hot microemulsion process. It was observed that CXB loaded SLN demonstrated a 45 percent rise in drug permeation compared to traditional gel, i.e. 31 percent, as well as a 2-fold rise in therapeutic activity compared to conventional gel and 70 percent release of drug in 48 h means it showed sustain release mechanism. The arthritis index was measured as CXB-SLN gel formulation was found to be very small (18.54%) relative to untreated (187.34%) and traditional gel-treated (91.61%) animals with CFA mediated arthritis (Nirbhavane *et al*., 2018). Shaji *et al.* prepared silica-coated solid lipid meloxicam nano-particles using melt emulsification ultrasound homogenization technique as indicated by high drug trap performance, four-transforming IR spectroscopy, and XRD powder tests. The release of lipid nano-particles showed a biphasic pattern of production, with high processing stability. A distribution system based on meloxicam nano-carrier potentiates the free radical blocking effects. A delivery system based on

meloxicam nano-carriers potentiates its free radical blocking performance and further improves its clinical effectiveness in rheumatoid arthritis treatment (Shaji *et al.,* 2013). In another study, *Ocimum sanctum L.* leaf extract loaded lipid carriers for deliverance of ursolic acid, a potent anti-inflammatory, analgesic and anti-arthritic agent. The mean particle size, zeta potential, polydispersibility index was found to be 120 nm, -27 mV, ~0.162. It was concluded that OLE-NLC loaded UA was contrasted with other branded formulations (diclofenac gel), and OLE-NLC demonstrated extended release of UA from NLC, higher product permeation performance such as 2.69, and also supports radiological analysis and molecular docking studies (Ahmad *et al*., 2018). Zhao *et al* prepared NLC loaded DXM using solvent evaporation technique using lipoid E80, and increased low water solubility of DXM by loading drug into NLC using complex phospholipids. Finally prepared DPC loaded NLC was contrasted with DXM loaded NLC and it was concluded that prepared DPC loaded NLC displayed higher entrapment efficiency, drug loading efficiency and an average particle size of 89.82 ± 1.64%, 2.13 ± 0.13%, 189.33 ± 0.58 nm and even in vitro release profile displayed delayed release velocity relative to free DXM loaded NLCs (Zhao *et al.,* 2012). Nabumetone loaded NLC was formulated using ultrasonic process Lipid phase to improve the potency of Nabumetone and it was observed that NBM-NLC exhibited burst release accompanied by continuous release and had particle size (127 ± 1.75 nm), polydispersibility index (0.279 ± 0.016) and also as in the NBM-NLC DSC thermogram, the drug's endothermic value at 84.04 °C has been shown to be fully soluble in the lipid. It was found that NBM-NLC had an anti-inflammatory activity 2 times stronger compared to NBM treatment (Kawish *et al*., 2017). Ultra-sonication technique was used to prepare ketoprofen/ naproxen loaded lipid nanoparticle using Lipid phase and it was concluded that drug loaded nanoparticle showed augmented in penetration and accumulation of drug in deeper layer (horny layer) as compared other marketed formulation of ketoprofen and naproxen (Puglia *et al.,* 2008). Another group of researcher synthesized nano-composites of triamcinolone acetonide-loaded hydroxyapatite by chemical precipitation process for treatment of arthritis in rats and further nano-composites of triamcinolone acetonide-loaded hydroxyapatite (TA-loaded HAp) by impregnation technique using lipid phase. The estimate involved cytotoxicity, paw diameter, haematological parameters and histological tests, particle size 70.45 nm, pore size 2.71 nm and product loading 41.94%. It was reported that TA-charged HAp nano-composites displayed a decline in release rate profile relative to pure dug for the volume of paw as well as haematological and histopathological anomalies in the adjuvant-induced arthritic rats (Jafari *et al.,* 2016).

Table 1 : Recent studies in development of NLC-based formulation for Rheumatoid Arthritis

Drug	Polymer; Lipid phase; Solvent; Surfactant	Dosage form	Method of preparation	Reference
Methotrexate	Carbopol 934; Stearic acid, Gelucire, Transcutol P; Dimethyl formamide, isopropyl alcohol	Gel	Hot micro-emulsion	Garg *et al*., 2016
Flurbiprofen	Lecithin; Compritol ATO 888, Miglyol 812; Water; Poloxamer 188, tween 80	Gel	Hot high pressure homogenization	Han *et al*., 2008
Tripterine	Precirol ATO-5 and Labrafil M 1944CS; Distilled water, Acetone, Ethanol; d-α-tocopherol, Sodium lauryl sulphate, polyethylene glycol succinate 1000	-	Solvent evaporation	Chen *et al*., 2012a
Dexamethasone	Polyoxyethylene 40 stearate, carrageenan; Lipoid E80; Glycerol trilaurate, Solutol HS 15	-	Probe sonication	Zhao *et al*., 2013
Diflunisal	Carbopol 934; Compritol 888 ATO; Oleic acid	Gel	Solvent-evaporation	Kaur *et al*., 2017
Dexamethasone acetate	γ-carrageenan; Compritol 888 ATO and soybean oil; Distilled water; Pluronic 188	-	Emulsification-ultrasound	Xu *et al*., 2011
Celecoxib	Carbopol 934; Phospholipon 90G; Tween 80, Transcutol; Water	Suspension	Hot micro-emulsion	Nirbhavane *et al*., 2018
Meloxicam	Aerosil 300P; Lutrol F 68 Sodium cholate, thiobarbituric acid, ethylene diamine tetra acetic acid and deoxyribose, Hydroxylamine hydrochloride and naphthylethylene diamine dihydrochloride; Diethylene glycol monoethylethe	-	Melt-emulsion ultrasound homogenization	Shaji *et al*., 2013
Ursolic acid	Carbopol-934; Glyceryl monostearate; Water, Ethanol; Tween 80,	Gel	Solvent evaporation	Ahmad *et al*., 2018
Dexamethasone	Lipoid E80, Miglyol 812N; Glycerol tri-caprylate, oleic acid, n-octanoic acid; Solutol H15, glycerol trilaurate	-	Solvent evaporation	Zhao *et al*., 2012
Nabumetone	Glycerylmonostearate, Oleic acid; Double distilled water; Tween 80	Pellets	Melt emulsification/ ultra-sonication	Kawish *et al*., 2017
Ketoprofen	Xanthan gum, Carbopol 934P; Miglyol 812, Compritol 888 ATO; Water; Lutrol F68	-	Ultra-sonication	Puglia *et al*., 2008
Triamcinolone acetonide	Calciumhydroxide, Polyvinyl alcohol; 3-(4,5 dimethylthiazol-2-yl) 2,5-diphenyltetrazolium bromide; Complete Freund's adjuvant	-	Chemical precipitation	Jafari *et al*., 2016

Application of NLCs in Pain Therapy

Puglia *et al* synthesized NLC by ultrasonic process charged benzocaine and lidocaine and tested using various techniques such as DSC (differential Calorimetry scanning) PCS (photon correlation spectroscopy) and it was concluded that NLC displayed greater penetration through, lower flux, and extended anaesthetic benefit (Puglia *et al*., 2011). Another research studied ibuprofen loaded NLC synthesized by hot pressure homogenization for the treatment of

osteoarthritis and other musculoskeletal disorders and assessed the potency of the NLC loaded drug. Raman spectroscopy and Fourier infrared transformation study confirmed rapid compound dissolution with no change in the peaks. It was hypothesized that IBU-NLC displayed improved skin penetration and thus improved effectiveness to relieve inflammation of the chronic joints (Suto *et al*., 2016). Another researcher group investigated NLC gel filled with lidocaine using lipid phase extrusion technique using hot melt. Various measurement parameters such as particle size less than 50 nm and dispersity index < 0.3 are tested, trapping capacity of drug-charged NLCs has been found to be 73.9 percent (Ajinkya *et al*., 2017). It was examined that artemether used to treat malaria displayed poor water solubility, the solubility of which was improved by formulation ARM loaded NLC using lipid process. It was observed that particle size and entrapment efficiency was found to be 63±28 nm and 30 ± 2%, respectively and release drug in a sustained manner and lower haemolytic potential (almost 13%). It was found that nanoject survival was higher compared with other preparations, such as oil (Joshi *et al*., 2008). Liu *et al* 2011 synthesized docetaxel-loaded NLCs using modified film ultra-sonication-dispersion method. The effectiveness of DTX-NLC in vivo anti-tumour and in vitro cytotoxicity was assessed. Apoptosis % was measured using the Duopafei or DTX-NLC-induced AnnexinV-FITC package. It was concluded that as drug dosage decreases the inhibition levels of NLC and DTX-NLC were found to be 42.74%, 62.69% and 90.36% (Liu *et al*., 2011). In recent research, modified hyaluronic acid (HA), bupivacaine (BPV) was prepared using combination of lipid melt-emulsification technique and solvent injection technique to fill NLCs. It was concluded that the formulated formulation demonstrated particle size (150 nm) and zeta-potential (- 40 mV), 90 percent of medication displayed excellent stability and performance in medication encapsulation. Comparable to free BPV and BPV-NLC, It was found that percutaneous penetration increase of BPV / NLCs and HA-BPV was 1.6 and 2.5 fold relative to free BPV (Yue *et al*., 2018). Dibucaine improved by loading a drug into NLC and SLN using high pressure, hot homogenization technique and mean diameter, and negative zeta potential was found to be 180 nm (-25 to 46 mV) in recent study with poor bioavailability and poor aqueous solubility of local anaesthetic (Barbosa *et al*., 2018). LBL-coated NLC (LBL-LA/NLCs) used to distribute nano-sized agents in pain therapy were studied and concluded that (LBL-LA / NLCs) showed improved durability and longer time of release ion action compared with free medication (Zhang *et al*., 2016). Ketorolac charged NLC were synthesized by phase transition process emulsification using carbomer 934 P, oleic acid, propylene gycol, labrafac and carbomer gel and found that the formulated nanocapsule had improved anti-inflammatory efficacy in the rat paw edema model caused by aerosil compared with other formulations on the market (Varshoaz *et al*., 2011). Another group of researchers researched that transcriptional trans-activator peptide (TAT) modified lidocaine loaded NLC were prepared by a lipid process using an emulsion evaporation-solidification system to enhance trans-dermal delivery of anaesthetics. Effects are measured in vitro in vivo using Franz diffusion cell. Mean diameter and encapsulation efficiency was determined to be (157.9 nm), (81.8 percent). Comparatively, it was found that the drug charged with NLC has higher trans-dermal fluxes, improves skin permeation and decreases discomfort more effectively (Wang *et al*., 2016). ARM-LFN nano-structured were synthesized using lipid carriers by using microemulsion modelling methodology. Through carrying out multiple validation experiments, it was found that the ARM-LFN NLC has demonstrated improved reliability, effectiveness and sustained release kinetics (Prabhu *et al*., 2016). In a study, NLCs loaded with ropivacaine (RPV-NLCs), using low-temperature process of emulsion evaporation-solidification and observed that zeta potential, drug loading, entrapment efficiency and particle size are -40.2±3.3 mV, 2.95±0.37 percent, 81.45±2.16 percent are 203.5±1.2 nm. Compared to control groups (mice writhing test); it was observed that RPV-NLCs displayed an improvement in inhibition intensity (89.1%) and a decrease in writhing reaction (Chen *et al*., 2015). In another study, Tripterine NLCs were prepared using d-α-tocopherol, polyethylene glycol succinate, soybean lecithin and Pluronic F-68 using solvent evaporation technique used to track skin disorder. Cationic, anionic, and neutral NLCs 'encapsulation efficiencies were 64.3±5.1, 67.8±4.4, and 72.5±4.9, particle size 90.2±9.7, 87.8±7.4, and 84.5±10.2 nm. In vitro experiments demonstrated delayed release of tripterin, and cationic NLCs > anionic NLCs > neutral NLCs were in the order of skin permeation. In vitro cytotoxicity experiments have shown that cationic NLCs have the maximum inhibition ratio (P<0.05) in B16BL6 (melanoma) cells (Chen *et al.,* 2012b). Kurana *et al.* synthesized meloxicam-charged lipid carriers (MLX-NLC) and researched the MLX-NLC gel on modification in skin's lipid profile to gain an insight into its role for improving skin penetration. Nanogel demonstrated outstanding thermal stability at 4±2°C. It was found that NLC gel to be a viable carter method for application of MLX topically (Khurana *et al*., 2015). In this study, complexation of Oxaprozin-cyclodextrin (CD) and the complex loading of lipid phase-Labrasol into nano-carriers using thin layer evaporation technique. In artificial membrane, various functional studies have shown combined utilization of liposome and CD. NLC has endorsed drug permeability to increase (16 and 8 times) and plain drug liposomal or NLC dispersion. It was also concluded that permeability of drug-cyclodextrin (CD) complexation increase 12-24 fold as compared to plain formulation (Mennini *et al*., 2016). Moghddam *et al* prepared nimuslide NLCs using lipid phase by melt emulsification ultrasound dispersion method. Mean particle size, entrapment capacity, Higuchi release kinetics R2 value was observed to be 214.4±11 nm and 89.4±3.40 percent, 0.984 and delayed release kinetics were seen in the in vitro release test. It was hypothesized that NLCs are talented method for nimuslide delivery topically (Moghddam *et al*., 2016). Ibuprofen (IBU)-loaded NLC using lipid phase (Precirol ATO 5, Miglyol 812, oleic acid), were synthesized using hot pressure homogenization technique. The zeta potential, PDI and particle size was found to be -15.40 to -7.54 mV, 0.065 and 0.237, 129–160 nm (Sütő *et al*., 2015). Recent study investigated that thymol showed antimicrobial, antioxidant and antiseptic properties and used to treat inflammation and wound healing. NLC filled with thymol was prepared using lipid butter and calendula oil. Particle size, zeta potential and entrapment efficiency was found to be 107.7±3.8 nm, -11.6±2.9 mV, and 89.1±4.2%. It was concluded that thymol loaded NLC showed anti- psoriatic action as well as better anti-inflammatory action as compared to negative control (Pivetta *et al*., 2018). Durán-Lobato *et al*

prepared cannabinoid derivative CB13 loaded lipid nano-particles (LNP) using emulsification-solvent evaporation technique using lipid phase (soya lecithin) and The cannabinoids have been confirmed to be effective agent for treating chronic pain (Durán-Lobato *et al*., 2016).

Table 2 : Recent studies in development of NLC-based formulation for pain treatment

Drug	Polymer; Lipid phase; Solvent; Surfactant	Dosage form	Method of preparation	Reference
Benzocaine and lidocaine	Compritol 888 Miglyol 812; Solvent; Lutrol F68	Hydrogel	Ultrasonication	Puglia *et al*., 2011
Ibuprofen	Carbolpol 973; Witepsol E85, Miglyol 812; Lutrol F68	Suspension	Hot high-pressure homogenization	Suto *et al*., 2016
Lidocaine	Cetyl esters wax NF, Carbomer 940; Labrafaclipophile WL 1349; Propylene glycol USP, Acetonitrile, Methanol; Tween 80	Gel	Hot-Melt Extrusion	Ajinkya *et al*., 2017
Artemether	Polyethylene glycol, Cremophor EL, Solutol HS 15; Oleic acid, seasame oil, sunflower oil and cotton seed oil; Acetonitrile; Tween 80, Glyceryldilaurate, Capmul MCM	Nano-inject dosage	Emulsification	Joshi *et al*., 2008
Docetaxel	Soya lecithin; Stearic acid, Glycerylmonostearate, Pluronic F68, Oleic acid	Gel	Modified film ultra-sonication dispersion	Liu *et al*., 2011
BPV	Precirol ATO, Compritol 888 ATO (100 mg); Distilled water, hylouronic acid; Polysorbate 80	Gel	Lipid melt-emulsification	Yue *et al.,* 2018
Dibucaine	Myristylmyristate, Cetylpalmitate; Liponate GC; Acetonitrile, Orthophosphoric acid, Triethylamine; Poloxamer 188	Gel	High pressure, hot homogenization	Barbosa *et al*., 2018
Lidocaine	Chitosan; Glycerylmonostearate, Cetyltrimethyl ammonium bromide; Hylournic acid; Miglyol912N	Gel	Layer by layer encapsulation	Zhang *et al*., 2016
Ketorolac	Labrafac; Polyethylene glycol hydroxyl stearate, Lecithin	Suspension	Emulsification and dilution	Varshoaz *et al.,* 2011
Lidocaine	Distearoyl phosphatidyl ethanolamine-(polyethylene glycol)-2000-maleimide; Soybean phospholipid, Polyoxyl castor oil, Labrafac PG; Ethanol, Distilled water; Tween 80	Gel	Emulsion evaporation-solidification	Wang *et al*., 2016
Artemether-Lumefantrine/Artesunate	Capmul MCM; Oleic acid, Solutol HS 15; Glyceryldilaurate, Tween 80	Injection		Prabhu *et al.,* 2016
Ropivacaine	Glyceryl monostearate; Soya lecithin, Solutol HS15; Chloroform, Acetone	Gel	Emulsion evaporation-solidification	Chen *et al*., 2015
Tripterine	d-α-tocopherol polyethylene glycol succinate, Soybean lecithin; Acetone, Ethanol; Pluronic F68	Gel	Solvent evaporation	Chen *et al*., 2012b
Meloxicam	Carbopol 940; Cetylpalmitate, Caprylic acid; Distilled water, Propylene glycol; Tween 80	Gel	Stirring and mixing	Khurana *et al*., 2015
Oxaprozin	Precirol ATO 5; Labrasol; Tween 80	Gel	Thin layer evaporation	Mennini *et al*., 2016
Nimesulide	Lecithin; Oleic acid, Stearic acid; Isopropyl alcohol, Methanol, Ethanol; Poloxamer 188	-	Melt emulsification ultrasound dispersion	Moghddam *et al*., 2016
Ibuprofen	Witepsol E 85; Precirol ATO 5, Miglyol 812, Oleic acid; Compritol 888 ATO, Cremophor RH 60, Poloxamer 188, Tween 80, Cetylpalmitate	-	Hot high-pressure homogenization	Sütő *et al*., 2015
Thymol	Carbopol 940; Illipe butter and Calendula oil; Pluronic F68	-	Hot emulsification	Pivetta *et al*., 2018
Cannabinoid	Compritol 888 ATO or Precirol; Soya lecithin; Polysorbate 20; Dichloromethane	-	Emulsification-solvent evaporation	Durán-Lobato *et al*., 2016

Conclusion

Globally, rheumatoid arthritis and pain disorders are a primarily growing medical issue that leads to physical injury and reduced living standards. NLCs provide an exciting potential as innovative strategies to improve the efficacy and safety of medications widely used for rheumatoid arthritis and pain relief. Comprehensive review of the NLC formulations revealed that NLCs may be seen as a effective approach for the therapy of rheumatoid arthritis and pain management in this progressive world.

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Conflict of interest

The authors declare no conflict of interests.

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