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 nanoparticles (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](image-url)
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).

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. 2*: Advantages of NLC as drug delivery system

*Fig. 3*: Classification of NLCs
Materials used for the synthesis of NLCs

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

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](image)

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 recrystallized 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).
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).

- Joints pain, inflammation and stiffness
- Affect the bone, cartilage, ligament and muscles
- Cause the abnormal remodelling of the sub-articular bone, weakening of periarticular muscles
- Narrowing of joints, cyst development

- Involves stiffness, inflammation of spinal cord, and also loss of spinal mobility
- Causes the back pain particularly at the lower limb
- Involves the triggering of many diseases such as IBD, psoriasis, spondyarthitis
- Detected by the radiographic imaging

- Inflammation occur in the joints
- Severity of inflammation depends upon the bacteria etiology and host features

- Permanently damage the joints and cause disability
- Occur due to environmental as well as genetic factor

- Cause the joint damage, disability, and commonly occur in psoriasis patients

Fig. 5: Hot homogenization technique
Fig. 6: Cold homogenization technique
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).

**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, gelucre, 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 40°C 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 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 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). 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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 delivery 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 lipid 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 preparation 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

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

Application of NLCs in Pain Therapy

Puglia et al synthesized NLC by ultrasonic process charged benzocaina 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
ostearthritides 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 antemether 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 nanojet survival was higher compared with other preparations, such as oil (Joshi et al., 2008). Liu et al 2011 synthesized doctexail-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 Annexin-V-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 glycol, 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 anaeasthetics. 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, Triptine 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 (Kurana et al., 2015). In this study, complexation of Oxpazoin-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 (Sütö 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 nanoparticles (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

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

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 an 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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