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Review Article

Technological strategies for the preparation of lipid nanoparticles: an updated review

Stefan Stefanov[1], Viliana Gugleva[1], Velichka Andonova[1]

1 *Faculty of Pharmacy, Medical University of Varna, Varna, Bulgaria*

Corresponding author: Stefan Stefanov (stefan.stefanov@mu-varna.bg)

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Abstract

The concept of improving drug biopharmaceutical properties by proper selection of delivery system should begin with a rational choice of relevant dosage form, followed by the precise assessment of physicochemical compatibility between the drug delivery system (DDS) and the active pharmaceutical ingredient (API). Afterwards, according to laboratory availabilities, an efficient production method should be selected and, if possible, to take into account the opportunity for lab-upscale and prevailed industry research needs. Amid the vast diversity of nanostructured drug delivery carriers, lipid nanoparticles (LNs) stand out with their undeniable advantages like exceptive biocompatibility and multiplicity, and their importance as "green" derivatives for biochemical processes. Their distinctive structural properties also allow adequate protection of loaded APIs against chemical degradation in an aggressive biological environment and provide excellent resiliency in modifying drug release profiles. This review highlights different findings reported by the researchers worldwide over the years and focuses on the various production strategies and techniques for the preparation of LNs.

Keywords

active pharmaceutical ingredient, high-pressure homogenization, nanostructured lipid carriers, scale-up production, solid lipid nanoparticles

Introduction

The bioavailability of orally administered drugs depends on their solubility in the gastrointestinal tract (GIT) and their permeability across cell membranes (O'Shea et al. 2022). Lipid nanoparticles can overcome the intrinsic drawbacks of the used drugs, such as chemical instability in the surrounding environment, low aqueous solubility, low cell permeability (Tenchov et al. 2021). Biocompatibility and biodegradability of the lipids used in LN composition are features of LNs that define the growing interest and in-depth research on these drug delivery systems (DDSs) (Ghasemiyeh and Mohammadi-Samani 2018). Moreover, the methods used for their production can be low-cost, easy to upscale, and environmentally friendly (Khairnar et al. 2022).

LNs comprise a lipid matrix typically solid at body temperature (Musielak et al. 2022; López et al. 2023). Two types of LNs can be defined: solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs) (Nguyen and Duong 2022). SLNs are the first generation of LNs (Müller et al. 2002). The main reason for the development of SLNs is combining the benefits of different drug carrier systems, such as liposomes and polymeric nanoparticles (PNPs). Similar to liposomes and nanoemulsions, SLNs are built from physiologically well-accepted biocompat-

ible excipients such as lipids and fatty acids (Satapathy et al. 2021). Like PNPs, their solid matrix can effectively protect the loaded APIs against chemical degradation and provide the maximum flexibility in modeling the drug's release profile (Sivadasan et al. 2021; Tewari et al. 2022). NLCs are often classified as the second generation of LNs that can overcome the disadvantages of SLNs, such as low percent of drug loading and drug expulsion during storage (Mohammadi-Samani and Ghasemiyeh 2018; Javed et al. 2022). The quality of LNs as DDSs depends mainly on the lipid composition and the method of their production (Hald Albertsen et al. 2022). The used technological approach and the process parameters have to provide reproducibility, high drug loading, chemical stability of the used components, and physical stability of the prepared LNs (Lombardo and Kiselev 2022).

This review summarizes the different methods of preparation of LNs with a focus on the mechanism of obtaining LNs, advantages, disadvantages, and limitations of the approaches. The following preparation methods are reviewed: High-Pressure Homogenization (HPH), Hot high-pressure homogenization method (HHPH), Cold high-pressure homogenization method (CHPH), High shear homogenization (HSH) and ultrasonication method (US), Microemulsion method (MM), Membrane contractor method (MC), Phase inversion temperature method (PIT), Coacervation method (CV), Double emulsion method (DE), Microemulsion cooling method (MEC), Emulsification-solvent evaporation method (ESE), Emulsification-solvent diffusion method (ESD), Solvent injection method (SI), Supercritical fluid method (SCF), Particles from Gas Saturated Solution (PGSS) method and Gas Assisted Melting Atomization (GAMA).

SLNs versus NLCs

SLNs are nanoparticles (NPs) composed of a solid lipid core with a mean diameter between approximately 50 and 1000 nm (Mishra et al. 2018). These lipid structures may contain purified triglycerides, complex glyceride mixtures, or waxes solid at both room and body temperatures, stabilized by a suitable surfactant(s) (da Silva Santos et al. 2019).

It can be argued that SLNs are relevant carrier systems as an alternative to traditional colloidal carriers such as emulsions, liposomes, polymeric micro and nanoparticles and are advantageous lipid-based DDSs for various reasons (Seo et al. 2023), e.g.:

1. particle size is from nano to submicron scale after drug encapsulation;
2. they can be prepared using generally recognized as safe (GRAS) ingredients (physiological lipids or lipid molecules) and without the use of organic solvents (Paliwal et al. 2020);
3. the particles formulation process (e.g., HPH) can be performed at a lower cost and easily upscaled (He et al. 2019; Dhiman et al. 2021).

Therefore, these NPs bear the advantages of other nano lipid carrier systems, and overcome several of their disadvantages. For example, SLNs are similar to nanoemulsions, but they have a solid lipid core, unlike the liquid lipid version. As a result, drug mobility decreases in the solid lipid state compared with the oily phase, thereby enhancing the controlled release of loaded APIs (Duan et al. 2020). The addition of a surfactant coating can further improve LNs stability. An additional advantage is the production of SLNs in powder form, which may be incorporated into pellets, capsules, or tablets to develop drug delivery further (Mohammed et al. 2023).

Despite these advantages, SLNs suffer from a few limitations, such as low drug loading efficiency, drug elimination through polymorphic transition during storage, and relatively high water content of the dispersions (Jacob et al. 2022; Subroto et al. 2023).

The low drug loading capacity (LC) of conventional SLNs is caused by densely packed lipid crystal network, which allows insufficient drug incorporation (Zhong and Zhang 2019), by the level of solubility of the drug in the lipid melt, melt blend of drug and lipid melt, the polymorphic state of the lipid matrix, and the solid matrix lipid structure (Satapathy et al. 2021).

NLCs were created to overcome the negative features of SLNs. NLCs are usually composed of a mixture of liquid and solid lipids, making the matrix imperfect, hence capable to include more drug molecules than in SLNs (Scioli Montoto et al. 2020). Irrespective of the presence of liquid lipids, the NLCs matrix is solid at body/room temperature, and this state depends on the content of the liquid lipids (Elmowafy and Al-Sanea 2021).

NLCs can severely limit drugs' ability to migrate and prevent the particles from coalescing by the solid matrix compared to emulsions. NLCs have other significant advantages over SLNs, such as drug protection, low toxicity, biodegradability, ability to control the release process, and avoid organic solvents in their preparation (Chauhan et al. 2020; Tang et al. 2023).

Types of SLNs and NLCs

Based on the chemical structure of the APIs and lipid, nature and concentration of surfactants, the degree of solubility of the drug in the melted lipid, the production method, and the operating temperature, the SLNs and NLCs are classified into three types (Müller et al. 2002; Gordillo-Galeano and Mora-Huertas 2018).

Types of SLNs

Type I (Homogeneous matrix model)

In the homogeneous matrix model, the APIs are molecularly dispersed in the lipid core or positioned as amorphous clusters. The obtaining of SLNs Type I is a result of optimal ratios of APIs and lipids due to HPH techniques (Balamurugan,

and Chintamani 2018). According to their structure, SLNs Type I can possess controlled release properties suitable for incorporating different APIs, e.g., prednisolone, which can show release from 1 day up to weeks (Pandey et al. 2022).

Type II (Drug enriched shell model)

Distinctive about this model is the low API concentration in the melted lipid. When using the hot HPH technique, during the cooling of the homogenized nanoemulsion, initially, the lipid phase precipitates, leading to gradually increasing concentration of API in the remaining lipid melt with a raised fraction of solidified lipid. Thus is formed API-free lipid core. When API's solubility reaches its saturation level in the remaining melt, an outer shell encompassing both API and lipid begins to harden around this core (Sumera et al. 2017; Ezzati et al. 2018). The formed core contains only a small amount of API, therefore the described model is not suitable to achieve a modified (prolonged) drug release. It suits to obtain an immediate release of API, and also, the occlusive properties of the lipid core can be used (Ganesan and Narayanasamy 2017).

Type III (Drug enriched core model)

In this model, API molecules are solubilized in the lipid melt up to its saturation solubility. The cooling of the lipid emulsion causes the supersaturation of API in the lipid melt. Under these conditions, first crystallizes the used API. The continuous cooling process causes lipid recrystallization too, and this circumstance contributes to the formation of the membrane around the already crystallized API-comprised core. This model is suited for APIs, which meet the criteria for prolonging their release (Uner and Yener 2007; Wu et al. 2021).

Types of NLCs

Imperfect type (Imperfectly structured solid matrix)

The essence of this type is in the construction of a matrix with many free spaces, which can be filled by API molecules. This architecture is achieved by mixing solid lipids and a sufficient amount of liquid lipids (oils). The inclusion of components with different chain lengths such as fatty acids and a mixture of mono-, di- and triacylglycerols, does not allow the matrix to form NLC with a highly ordered structure, thus creating free spaces (structural imperfections) (Salunkhe et al. 2015; Xu et al. 2022).

Amorphous type (Structureless solid amorphous matrix)

This structure type is obtained by mixing some specific lipids (dibutyl adipate, hydroxy octacosanyl hydroxyl stearate, isopropyl palmitate), which do not recrystallize after homogenization and cooling of the nanoemulsion. These lipids form amorphous matrices and minimize the expulsion of API during storage (Salvi and Pawar 2019; Xu et al. 2022).

Multiple types (Multiple oils in fat in water)

The solubility of the lipophilic API in liquid lipids (oils) is higher than in solid lipids. This staging is used to develop the "multiple" type NLCs. In this approach, a higher amount of oil is blended in solid lipids. At low saturation, oil molecules are efficiently dispersed into the lipid matrix. The additional amount of oil leads to phase separation and the creation of oily nano compartments surrounded by the solid lipid sheath. This method allows the modeling of controlled API release. Furthermore, the lipid matrix prevents API expulsion. Lipophilic APIs can be solubilized in oils, and "multiple" types of NLCs could be formed during the cooling process after HHM (Borges et al. 2020; Akbari et al. 2022).

Methods of preparation

Different interesting chemical approaches and formulation techniques have been developed over the years for the synthesis of LNs. The most significant and challenging issues concerned with the green method selection can be detached as follows:

1. the energy needs for the method of synthesis and their optimization;
2. the specific energy constraints of the process.

High energy approaches

High-energy-based approaches include the use of equipment causing deformation under pressure, creating significant shear forces and severe mechanical forces, as well as applying other mechanisms to reduce particle size (Che Marzuki et al. 2019). In summary, high-energy processes can be identified in two main stages: (i) transformation of macrodroplets into smaller ones; (ii) the adsorption of a surfactant on their surface for the purposes of stabilization (Håkansson and Rayner 2018).

High-Pressure Homogenization (HPH) method

HHM is one of the most commonly exploited methods for the preparation of LNs, tightly bound to HPH (Huang et al. 2017). HPH is a suitable, reliable, and well-known method for producing different types of LNs. Besides, it becomes clear that this powerful method does not have scaling-up problems (Shirodkar et al. 2019). HPH has been used for a long time to produce nanoemulsions for parenteral nutrition (Azmi et al. 2019). It has currently been applied

for SLNs and NLCs production and represents the primary method adopted for these LNs (Yadav and Kale 2019). During the process, homogenizers push a liquid with high pressure (100–2000 bar) through a narrow size space (few μm). The liquid obtains high velocity (more than 1000 km/h) by enforcing high pressure, resulting in a break down the accelerated particles to submicron size, caused by generated shear stress and cavitation forces (Khosa et al. 2018). The used lipid content in this procedure is most often in the 5–10% range and does not cause technological problems. Data exist that even mixtures with higher lipid content (up to 40%) can be homogenized and brought to a nanodispersion state (Musielak et al. 2022).

The HPH technique was used for preparation of NLCs loaded with coenzyme Q10 at a throughput of 25 kg/h (Hu et al. 2016).

HPH method was reported to prepare efavirenz-loaded SLNs, characterized by improved drug bioavailability (vs. oral admintration) and brain targeting feasibility (Gupta et al. 2017). Enhanced bioavailability, along with lower dosing and side effects was reported also by Gorle et al. (2023), which applied the HPH method to incorporate the tyrosine kinase inhibitor axitinib in NLCs.

Hot High-Pressure Homogenization (HHPH) method

The process of HHPH takes place at temperatures above the melting temperature of the used lipid. The lipids and APIs are melted and combined with an aqueous surfactant at the same temperature. A hot pre-emulsion is formed by using the high-shear device (Jain and Thareja 2020). A representative for the process is the production of smaller particles due to decreasing viscosity of the internal phase due to high operating temperatures (Singh 2019). It is essential to be kept in mind that HHPH increases the temperature of the sample (approximately 108 °C for 500 bar) (Chandana et al. 2021). Finally, the obtained nanoemulsion is cooled to room temperature resulting in the lipid recrystallization and formation of nanoparticles (Qushawy and Nasr 2020).

Makoni et al. developed efavirenz-loaded SLNs and NLCs by the HHPH method and investigated the physical stability of the dispersions for two months at different conditions (25 °C/60% RH and 40 °C/75% RH). The optimal LNs formulation exhibited high entrapment efficiency (90%), sustained drug release and excellent physical stability at ambient temperature (Makoni et al. 2019).

HHPH method was applied to produce atorvastatin-loaded SLNs as potential self-administrable eye drop formulation with increased bioavailability in aqueous and vitreous humor and improved stability (Yadav et al. 2020). Also, celecoxib-loaded NLCs with PS of < 200 nm and sustained release were prepared for potential treatment of leukemia and breast cancer (Üner et al. 2019).

Recently, the hot homogenization process followed by ultrasonication was applied to achieve high drug loading (over 90%), entrapment efficiency (of 5%), and enhanced oral bioavailability of raloxifene with NLCs (3.19 – fold as compared to drug-free suspension in female Wistar rats) (Murthy et al. 2020).

Cold High-Pressure Homogenization (CHPH) method

CHPH has been developed in order to eliminate the problems appearing when applying an HHPH technique (Duan et al. 2020), to wit:

1. API degradation due to the high operating temperature;
2. API dispersal into the aqueous phase during homogenization;
3. Expressed variability after the nanoemulsion crystallization step.

CHPH, to some extent is similar to HHPH. API molecules are incorporated into the matrix by dissolving or dispersing in the heated and molten solid lipid. The API-containing lipid melt is rapidly solidified by cooling with dry ice or liquid nitrogen. The rapid cooling leads to homogeneous stowage of API inside the lipid material. Afterwards, grinding of the solid bases and obtaining of a fine powder of microparticles is achieved, which is subsequently dispersed in a cold aqueous surfactant solution. The resulting dispersion is subjected to HPH in order for SLNs to be generated (Salvi and Pawar 2019; Lammari et al. 2021).

Typical for CHPH is a process of solid lipids homogenization as opposed to a lipid melt in HHPH. Attainment to solid lipids' dispersion state requires high-energy input and strict homogenization conditions (Kovačević et al. 2020; Sastri et al. 2020).

Makhmalzade et al. (2021) prepared deferoxamine-loaded SLNs applying the CHPH method and a full factorial design to evaluate the impact of formulation constituents on the physicochemical properties of the nanoparticles. The optimal formulation was composed of Compritol/ oleic acid as solid/liquid lipid, Tween 80 and lecithin (surfactants), and exhibited narrow size distribution, high loading and sustained drug release. According to the authors, the selected method of preparation (CHPH) contributed to the observed high EE values (60%), as it restricts hydrophilic drugs' partition between lipid and aqueous phases.

In another study Duong et al. (2019a) investigated the effect of formulation parameters on ondansetron hydrochloride encapsulation in NLCs. As optimal CHPH conditions were estbalished: pressure (500 bars); cycles (6), leading to the formation of NLCs with high entrapment efficiency and prolonged ondansetron release (up to 96 h).

High Shear Homogenization (HSH) and/ or ultrasonication (US) method

HSH /US are actually dispersing techniques. LNs dispersions are obtained by dispersing the melted lipid in

a warm aqueous phase containing surfactants by a high shear homogenization followed by ultrasonication (Cheaburu-Yilmaz et al. 2019).

The technique primarily involves heating a solid lipid to approximately 5–10 °C above its melting point. The lipid melt is dispersed in an aqueous surfactant solution at the same temperature under high-speed stirring and an emulsion is formed. The following sonication reduces the droplet size of the emulsion. Gradual cooling of the warm emulsion below the lipid crystallization temperature yields LNs dispersion (Souto et al. 2019). HSH/US are successfully used to obtain dispersions of SLNs and NLCs without organic solvents with a tight particle distribution (Bazzaz et al. 2018; Jannin et al. 2018; Zardini et al. 2018).

HSH/US method was applied for insulin-loaded SLNs with improved stability (Ansari et al. 2017).

Recently, the technique of HSH followed by ultrasonication was used to prepare SLNs with improved solubility of total flavonoid extract from *Dracocephalum moldavica* L. with myocardial protective function (Tan et al. 2017). In another study, Ajiboye et al. (2021) investigated the effect of HSH/US on the properties of olanzapine loaded NLCs.

Shah et al. (2020) applied HSH (15,000 rpm for 10 min) followed by US (~3 min) to prepare optimized linagliptin-loaded SLNs that increased drug permeability and oral bioavailability by 3-fold compared to administered solution of linagliptin in rats.

The main advantages, disadvantages, and limitations of the high-energy approaches for LNs preparation are shown in Table 1.

Low-energy approaches

Low-energy-based methods do not consume a substantial amount of energy to obtain LNPs and sometimes are even spontaneous. The type of these techniques determines as thermal or isothermal. The thermal processes are characterized by emulsion formation due to temperature-dependent changes in surfactant properties. Specific to isothermal methods is the formation of an emulsion due to continuous temperature changes. Low-energy-based approaches are easy to use and cost-effective as they have the advantage to generate tiny droplets without specialized equipment (Chircov and Grumezescu 2019; Li et al. 2020).

Microemulsion (MM) technique

The formation of microemulsion as a phase of the production of SLNs and NLCs is reported in the early 90s (Gasco 1993). Distinctive for this method is the spontaneously formed microemulsion due to the high surfactants/lipid ratio. A few simple steps build this method. At first, it proceeds to melt the lipids and mix the melt with a hot surfactant solution thru a constant cautious stirring until the formation of a microemulsion. Then, the hot microemulsion is dispersed in a high volume of cold water (2–3 °C) under continuous moderate stirring. This operation leads to the solidification of the liquid droplets (Masiiwa and Gadaga 2018). The obtained SLNs and NLCs are spherical with a narrow size distribution. One of the drawbacks of the microemulsion technique is the high dilution level of the final dispersion (ranging from 1:25 to 1:50), which may require additional concentration. Another drawback is using a high concentration of surfactants/co-surfactants (Thepwatee et al. 2019).

Joshi et al. (2019) described the preparation of NLC-based gels from the microemulsion technique for drug delivery through the skin, particularly concerning the method of obtaining and the characterization of the final nanobased carriers.

Some cases for applying the microemulsion technique in preparing SLNs and NLCs formulations were reported such as methotrexate-loaded SLNs, characterized by small particles size (238 nm), excellent physical stability and controlled drug release (Krishnasailaja and Gazi 2023), as well as phytostanol ester-loaded SLNs serving as a promising DDS in the therapy of hypercholesterolemia (Shrestha et al. 2021).

In another study Ali et al. (2022) developed allopurinol-loaded NLC subsequently incorporated into hydrogels for potential treatment of gout. The formulated LNs served as feasible transdermal drug delivery platform, showing approx. 28-fold increase in skin penetration and superior anti-gout effect vs. free drug (Ali et al. 2022).

Membrane contactor (MC) technique

The technical setting for this method is the use of a cylindrical membrane module. The aqueous phase containing a surfactant flows from the inside of the membrane and the molten lipid is compressed through the pores of the membrane from outside to inside to pass into the aqueous phase (Fig. 1). This

Table 1. Advantages, disadvantages, and limitations of the high-energy approaches for LNs preparation.

Methods	Advantages	Disadvantages	Limitations	References
HPH method	Effective dispersing technique	Highly energy-consuming process. Unacceptable distribution of API into the aqueous phase.	High polydispersity	Musielak et al. 2022
HHPH method	Scalable, commercially available	Pass of API into the water phase during homogenization. API decomposition – temperature-induced. Complications in a result of the elaborate character of the crystallization step.	Not appropriate for thermolabile APIs	Ana et al. 2019; Hanifiyah et al. 2021
CHPH method	No temperature-induced API degradation or crystalline modification	No data	Not possible complete evasion of API exposure to high temperatures.	Joshi et al. 2019; Garg and Jain 2022
HSH and/or US method	Small particle size: 30–180 nm. Low shear stress.	Possible metallic contamination due to metal shading. Less entrapment efficiency. Energy consuming process.	During sonication, metallic contamination of the product may occur.	Jannin et al. 2018; Kelidari et al. 2018; Alarifi et al. 2020

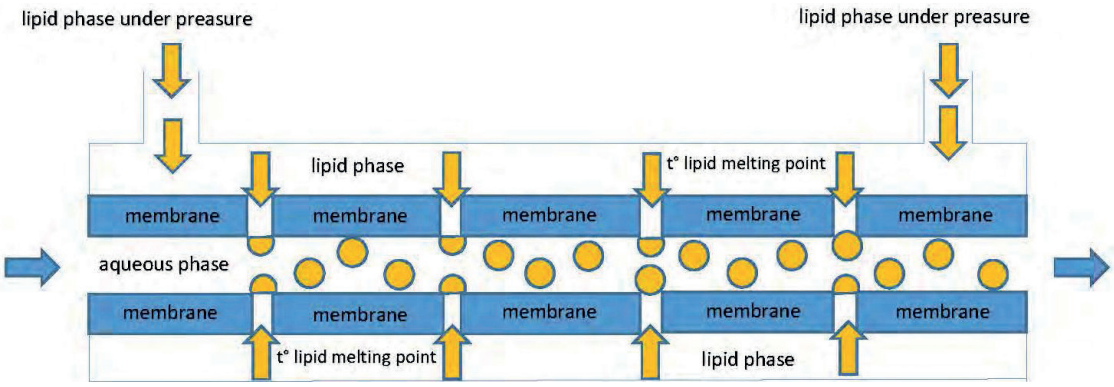

Figure 1. Schematic drawing of the process of preparation of LNs using a membrane contactor.

allows the formation of small droplets which are differentiated in the aqueous phase. The water is maintained at the lipid melting temperature. Then SLNs and NLCs are formed thru cooling at room temperature. The method is scalable and the particle size can be adjusted by using membranes with different pore sizes (Lombardo and Kiselev 2022).

Furthermore, the MC technique was applied to obtain SLNs with high vitamin E LC (Chaves et al. 2023).

Phase inversion temperature (PIT) technique

In practice, the transformation of an emulsion from O/W type to a W/O type is termed "phase inversion." It can be induced by changing the operating temperature. The temperature at which the inversion occurs is referred to as PIT (Jintapattanakit 2018). In essence, this technique depends on the change in the properties of polyoxyethylated surfactants at different temperatures. The Griffin's hydrophilic-lipophilic balance (HLB) value of surfactants is valid at 25 °C. At this temperature, the hydrophilic parts of the surface-active compounds are hydrated to a certain level. At elevated temperatures are observed dehydration of the ethoxy groups, which leads to the rising of the lipophilicity of the molecules of the surface-active compounds and HLB value decreases. The affinity of surface-active compounds to the aqueous and lipid phase is equal when the PIT has been reached. This particulate state is characterized by very low surface tension and intricate structures in the system. Further increasing the temperature rises enough the affinity of the surface-active compounds to the lipid phase, which allows stabilization of W/O type emulsions. If rapid cooling is applied, stable particles with desirable size and polydispersity can be obtained (Gomes et al. 2019).

Weerapol et al. (2022) developed quercetin-loaded SLNs characterized by small sizes, excellent physical stability, high entrapment efficiency values and sustained drug release. The selected PIT technique was reported as feasible approach to incorporate poorly aqueous soluble compounds into LNs, as confirmed also by Simão et al. 2020. The authors elaborated hesperetin-loaded NLCs with high entrapment efficiency (72.7%), narrow size distribution (PDI < 0.2), controlled drug release (up to 72 h) and excellent in vitro cytotoxic potential (Simão et al. 2020).

In another study, furosemide-loaded SLNs were synthesized by the PIT technique using 3^2 factorial design. The parameter sensitivity analysis demonstrated a pronounced effect of particle size and reference solubility on the $AUC_{0-\infty}$, C_{max}, and t_{max}. The results showed that the optimized formulation could provide a controlled release and improve the formulation's physicochemical stability for furosemide oral delivery (Ali and Singh 2018).

Coacervation (CV) technique

LNs can be produced by acidification of a micellar solution of fatty acid alkaline salts. At first, a stock solution of the polymeric stabilizer must be prepared by heating in hot water. The alkaline salt of the fatty acid is homogeneously dispersing in the polymeric stabilizer stock solution, heated to a precisely defined degree with constant stirring until a clear solution is obtained. Then addition of the API (commonly solubilized in ethanol) to the clear solution under permanent stirring is performed until establishing a single-phase state. The gradual input of a coacervating solution to this mixture formed a suspension. In the next step, the suspension is cooled in a water bath under permanent agitation until the launch of well dispersed and API-loaded NPs (Clemente et al. 2018).

The coacervation technique was applied to prepare quercetin-loaded SLNs with high drug loading, controlled release and preserved antioxidant activity of the encapsulated phytochemical (Talarico et al. (2021).

In another study Muntoni et al. (2019) used a fatty acid coacervation method to entrap peptides (insulin and an insulin analog) into NLCs for oral administration. The authors observed an optimized ex vivo and in vivo intestinal uptake of glargine insulin (the insulin analog) expressed by significantly higher permeation (till 30% dose/mL) than free peptide and approximately 6% absolute bioavailability.

Double emulsion (DE) technique

The preparation of SLNs and NLCs through a double emulsion technique is suitable for hydrophilic APIs and peptides. In this method, an APIs aqueous solution is emulsified in a melted lipid blend to form a primary W/O emulsion, stabilized with suitable excipients. Second, the

primary W/O emulsion is dispersed in an aqueous solution of hydrophilic emulsifier to form a double W/O/W emulsion. Finally, the double emulsion is stirred and isolated by filtration (Mazur et al. 2019).

Subroto et al. (2022) used the DE technique to prepare SLNs as promising DDS for ferrous sulfate, capable to overcome its low stability and unpleasant flavor. The prepared nanoparticles exhibited a spherical shape and high drug entrapment efficiency (Subroto et al. 2022). Doxycycline-loaded SLNs, prepared by DE technique, significantly decreased the Brucella melitensis loading within macrophages (3.5 Log) in comparison with the free doxycycline (Hosseini et al. 2019).

Microemulsion cooling (MEC) technique

John and Jay (2006) patented a micro emulsion-based method for the preparation of SLNs. This method essentially presents the preparation of o/w microemulsion, where the emulsifying wax is melted at 37–55 °C. At the next step, water heated to the same temperature is added under gentle stirring. As a result, a homogeneous milky suspension is formed. Then a suitable polymeric surfactant is added into water until a stable and clear o/w microemulsion in the form of a liquid matrix is produced. SLNs are molded by precipitation from already obtained and cooled o/w microemulsion at room temperature or 4 °C. As a benefit, this method is reproducible, simple, and easy to scale up. No organic solvents are used, and all components are biodegradable.

Kuo and Lee (2016) used the MEC technique to prepare etoposide-loaded SLNs grafted with 83–14 monoclonal antibody (8314MAb) and anti-epithelial growth factor receptor (AEGFR). The authors reported that incorporating both 8314MAb and AEGFR increased the particle size but decreased the zeta potential, etoposide release rate, and viability of HBMECs and HAs. In this regard, the conjugation of 8314MAb and AEGFR on etoposide-loaded SLNs can be a promising strategy to deliver antitumor etoposide to the brain and restrain the propagation of glioblastoma multiforme.

In their study Cirri et al. (2018) investigated the effect of methods of preparation (homogenization-ultrasonication and microemulsion cooling technique) on the main physicochemical characteristics of hydrochlorthiazide-loaded NLCs. The prepared LNs via the microemulsion method with subsequent cooling exhibited smaller particles size (within 300 nm to 400 nm diapason) higher EE values and prolonged drug release vs. the carriers prepared by the homogenization-ultrasonication method.

The discussed above low-energy approaches have distinct advantages and suffer from some disadvantages and limitations, which are briefly summarized in Table 2.

Approaches with organic solvents

Emulsification solvent-evaporation (ESE) technique

In general, this technique involves the following steps of preparation:

1. Preparation of organic phase: the lipophilic material is dissolved in an organic solvent (water-immiscible) by magnetic stirring.
2. Pre-emulsification step: the lipid-containing organic phase is dispersed in aqueous solution using a high-speed homogenizer.
3. Nano emulsification step: the coarse pre-emulsion in the fastest way was passed through a high-pressure homogenizer to obtain nanodispersion.

Table 2. Advantages, disadvantages, and limitations of low-energy approaches for LN preparation.

Methods	Advantages	Disadvantages	Limitations	References
Microemulsion technique	Low energy input. Expected potential stability.	Very sensitive to change. Intensive formulation work. Low NP concentration.	A strong dilution of particle suspension due to the use of the large volume of water. A high concentration of surfactant and co-surfactant is not desired.	Mohd et al. 2018; Mazur et al. 2019; Nsairat et al. 2021
Membrane contactor technique	Possible large-scale production. Control of size. Cooling at room temperature.	Obstruction of the membrane.	Particle size is highly influenced by the type and concentration of surfactants added to the formulation. Limitations concerned with the transmembrane pressure.	Khan et al. 2016; Bhatt et al. 2018; Nsairat et al. 2021
Phase inversion temperature technique	Low energy input. Solvent-free. Suitable for heat-bearing molecules.	The incorporation of additional molecules influences the inversion. Instability of emulsion.	Burdensome technique.	Ali and Singh 2018; Gomes et al. 2019
Coacervation technique	Suitable for lipophilic APIs (by solubilizing in the micellar solution after coacervation). Suitable for hydrophobic ion pairs of hydrophilic APIs. Solvent-free technique. Simple to scale-up technique. Monodispersity.	Not suitable for pH-sensitive drugs	pH-dependent technique	Battaglia et al. 2017; Clemente et al. 2018
Double emulsion technique	Possibility for surface modification and incorporation of hydrophilic molecules.	Relatively large particles. Coalescence of the internal aqueous droplets within the oil phase, the coalescence of the oil droplets, splitting the surface layer of the internal droplets.	Instability associated with multiple emulsions.	Mazur et al. 2019; Jain and Thareja 2020; Subroto et al. 2022
Microemulsion cooling technique	Reproducible method. Simple and easy to scale up. Use of biocompatible ingredients.	Surfactants may cause hypersensitivity reactions.	Suitable for IV, IM, or subcutaneous administration.	Singh 2019

Formed nanodispersion is kept on the magnetic stirrer for a relatively long time (commonly overnight), sometimes in a fume hood, to drive the organic solvent. Upon solvent evaporation, nanodispersion is formed by the precipitation of lipid material in the aqueous medium. Solidified nanodispersion is filtered through a glass filter in order to remove lipid and API agglomerates (Chaudhary et al. 2021).

The emulsification solvent-evaporation method was used to prepare SLNs for the improvement of oral bioavailability of ramipril (Vakhariya et al. 2019). Also, SLNs prepared by the same technique with glyceryl monostearate and poloxamer 407 have enhanced bioavailability with sustained release of irbesartan being an attractive approach for oral administration of the drug (Soma et al. 2017).

Emulsification solvent-diffusion (ESD) technique

A certain amount of solvents, partially soluble in water, such as butyl lactate, isobutyric acid, benzyl alcohol, tetrahydrofuran, and isovaleric acid are used to solubilize the solid lipids in the preparation of LNs. Transient O/W emulsion is passed into water under prolonged stirring, which leads to solidification of the dispersed phase and forming LNs due to diffusion of the organic solvent. Typical O/W ratios are 1/5 or 1/10 (Chaudhary et al. 2021).

The ESD technique was used to prepare SLNs for topical delivery of tretinoin (Patravale and Mirani 2019).

In another study, tenofovir disoproxil fumarate-loaded NLCs, obtained via the same method were reported, characterized by sustained drug release, and suitable physicochemical characteristics to achieve nose to brain delivery (Sarma and Das 2019).

Solvent injection (SI) technique

The principle of the SI method is very close to that of the solvent-diffusion method. When the solvent injection technique is applied, lipids are mixed with a water-miscible solvent or mixture of solvents (e.g., acetone, isopropanol or methanol) and after that is immediately injected into an aqueous solution of surfactants through an injection needle (Schubert et al. 2003).

Two parallel and simultaneous circumstances lead to the effective formation of SLNs and NLCs: Firstly, diffusion of the solvent out of lipid-solvent droplets into the water causes a reduction of their size and increases lipid concentration. Secondly, the diffusion of pure solvent from the lipid-solvent droplet reduces the size of droplets. Obtaining SLNs and NLCs can be influenced by the control of technological parameters such as lipid concentration, lipid concentration in the solvent phase, injected solvent, injected volume of solvent, and viscosity of the aqueous phase (Lakshmi and Joni 2021).

Elvitegravir-loaded SLNs with improved drug aqueous solubility (800–1030-fold vs. free drug) were successfully prepared via the SI technique (Kommavarapu et al. 2015).

In another study Duong et al. (2019b) used the SI technique to encapsulate the hydrophilic ondasetron hydrochloride into NLCs. The prepared LNs were characterized by high entrapment efficiency (more than 90%), narrow size distribution and sustained drug release.

Supercritical fluid (SCF) technique

The production of LNs from emulsions using SCF technology is referred to as "supercritical fluid extraction of emulsions" (SFEE). The organic solution is prepared by solubilizing the lipid and the API in an organic solvent (e.g., chloroform) with a suitable surfactant followed up by dispersing this organic solution into an aqueous solution (with or without co-surfactant). The mixture is passed through a high-pressure homogenizer in order to be formed an O/W emulsion. The obtained O/W emulsion is fed from the one end of the extraction column (usually the top) at a constant flow rate. The SCF, maintained at constant temperature and pressure, is fed counter-currently at a constant flow rate. The LN dispersions are formulated by the continuous extraction of solvent from the O/W emulsions (Akbari et al. 2020).

Couto et al. (2017) applied the SCF technique for preparing vitamin B2-loaded SLNs, characterized by controlled API release, high EE, bioactive load, and proper API protection. In their study Andrade et al. (2019) developed praziquantel-loaded SLNs, characterized by decreased lipid (cetyl palmitate) crystallinity and high (83%) entrapment efficiency as result of the applied SCF technique for LNs preparation.

Particle from Gas Saturated Solution (PGSS) method and Gas Assisted Melting Atomization (GAMA) method

PGSS method consists of the melting of the material, which dissolves the SCF under pressure. It is performed incorporation of CO_2 in melted or liquid suspended substance(s), leading to a gas-saturated solution/suspension that is further expanded through a nozzle with the formation of SPs or droplets (Melgosa et al. 2019). The substances do not need to be soluble in CO_2. Some of the most crucial PGSS expedients applied to lipid NPs are the so-called Gas Assisted Melting Atomization (GAMA). Lipids are placed in a thermostated mixing chamber (MC), where they are melted and kept in contact with SCF CO_2 at selected conditions. Then, the saturated lipid fluid is forced through a nozzle by opening the valve at the bottom of the MC to produce NPs. NPs are gathered by a collection device and dispersed in water by vortexing and sonicating to obtain suspensions. Polyethylene glycol (PEG) can be added to the formulation to increase the dispersion rate in water (Chakravarty et al. 2019).

Pedro et al. (2016) developed curcumin-loaded SLNs via PGSS method characterized by homogenous size distribution, high loading and preserved drug's chemical stability.

The discussed technological methods that use organic solvents with their remarkable advantages, the main disadvantages, and limitations are summarized in Table 3.

Table 3. Advantages, disadvantages, and limitations of approaches that use organic solvents for LNPs preparation.

Methods	Advantages	Disadvantages	Limitations	References
Emulsification-solvent evaporation technique	Small particle size ≤ 24 nm. Avoidance of heat. A low viscous system is formed. Low-energy input. NPs obtained are monodisperse and with high encapsulation efficiency. Appropriate for thermolabile drugs. The process can be automated and scaled-up.	Low dispersing degree. Instability of emulsion. The insolubility of lipids in organic solvents. Additional solvent removal procedure.	Production of very dilute nanodispersion is not required. An additional step is required. e.g., ultrafiltration or evaporation. The organic solvent may remain in the final preparation.	Duong et al. 2020; Chaudhary et al. 2021
Emulsification solvent diffusion technique	Avoidance of heat during the production procedure. Lipids are dissolved in a partially miscible solvent, e.g., benzyl alcohol, tetrahydrofuran.	Harsh processing conditions. Instability issues. Use of organic solvents and needs of the additional removal procedure.	Ultrafiltration or lyophilization techniques are required. The residue of organic solvent may remain in the final preparation.	Patravale and Mirani 2019
Solvent injection technique	Secure handling and fast production process. Lipids are dissolved in a water-miscible solvent, e.g., ethanol, methanol, acetone without using a sophisticated instrument (e.g., high-pressure homogenizer).	Low dispersing degree. Instability of emulsion.	The residue of organic solvent may remain in the final preparation.	Lakshmi and Joni 2021
Supercritical fluid technique	Particles are obtained as a dry powder. Avoid the use of solvents; in preference to suspensions. Mild temperature and pressure conditions. Carbon dioxide solution is an excellent choice as a solvent.	Costly method.	The residue of organic solvent may remain in the final preparation.	Akbari et al. 2020
Particle from Saturated Solution method and Gas Assisted Melting Atomization method	Produced fine and non-agglomerated low-density powders. Suitable operating conditions for protein-loaded lipid submicron particle preparation. High protein loading. The GAMA process does not involve the formation of emulsions or microemulsions.	Typically, PGSS produces large-sized particles with broad distribution profiles. Ultrasonic and coaxial nozzles applied to PGSS have been found to provoke the denaturation of fragile proteins.	The different physicochemical properties of components may result in poor, large, inhomogeneous particles. Low stability and embarrassing drug release profiles.	Milovanović and Lukić 2022

Drug release

There are many studies about API incorporation in LNs, but less data exists about API release. Tracing of API incorporation and subsequently release from LNs gives us an appropriate tool for design, development, and evaluation of these prospective DDS. The drug release from LNs is compromised between the composition and the structural model provided for each formulation. API incorporated into LNs are usually released by degradation and surface erosion of the lipid matrix and by diffusion of API molecules through the lipid matrix (Alsulays et al. 2019). API release from LNs could be directed utilizing different models and relevant media. Excised skin, artificial membranes, or different tissue constructs can be used as practical barriers. A severe problem met at LNs is the observed burst release. There is a possibility of modifying the release profiles by modifying the lipid matrix, change in surfactant concentration and production parameters, or surface modification (Zelepukin et al. 2022).

API release from LNs is determined by API localization:

1. Localization of the API within the core of a solid lipid matrix offers the possibility to obtain a prolonged release.
2. Localization of API molecules on particle surface often leads to burst effect (fast initial release). LNs can show a biphasic drug release profile: an initial burst release, due to the API localized at the surface, which is followed by a more gradual release due to the API localized into the lipid matrix.

The extent of release can be operated by controlling API solubility in the aqueous phase during production as well as by directly changing the process temperature and the surfactant concentration. Higher temperatures and higher surfactant concentrations increase the burst effect. Room temperature production avoids the API's segregation into an aqueous phase and subsequent repartitioning into the lipid phase without burst release. To avoid or minimize the burst release, LNs can be produced surfactant-free or with surfactants unable to solubilize the API. The release kinetics depends on the release conditions i.e. sink or non-sink, release medium, etc. (Rahnfeld and Luciani 2020).

Conclusion

The development of versatile API delivery systems suitable for different administration routes as topical, oral, pulmonary, ocular, and parenteral is of interest to the pharmaceutical industry. LNs are contemporary formulations that offer much more flexibility in drug loading, optimal release profile, and improved efficacy in producing final dosage forms. The results obtained with their dermal application are encouraging, and presumably this can be one of the main applications of LNs in the future. This application is promising in developing and using phytomedicines because of the difficulties in their delivery due to their physicochemical properties. The excipients used for LNs production have GRAS status, and most of them have already been incorporated in the pharmaceutical or food products. The easy scale-up of the formulation technique is also a fundamental feature of the LNs' preparation process. However, technologists still face the challenge of minimizing the burst effect of APIs included in LNs. Other areas for further research include LNs' surface modification to achieve target selectivity as well

as the possibility to include more than one API in LNs developing thereby nanocarriers with optimal physicochemical characteristics.

Conflict of interest

No conflict of interest to report.

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