IJPPR
INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals
ISSN 2349-7203
HUMAN

Human Journals
Review Article
November 2022 Vol.:25, Issue:4

Nanostructred Lipid Carriers – A Promising Approach to Oral Drug Delivery System

IJPPR
INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals
ISSN 2349-7203
HUMAN

Mhetre R.M*., Tiwari B.D., Varsha Tegeli, Lavate A.B., Jadhav R.I.,

Amepurva Forums Dr. Ashok Gujar College of Pharmacy, Boramani, Solapur, Maharashtra, India.

Submitted: 25 October 2022
Accepted: 31 October 2022
Published: 30 November 2022

HUMAN JOURNALS
www.ijppr.humanjournals.com

Keywords: NLC, Solid lipid nanoparticles, solvent evaporation.

ABSTRACT

Nanoparticles are defined as colloidal particulate systems having dimensions between 10-1000nm. NLCS are prepared from solid lipid, liquid lipid, surfactant, active ingredients &water. Biodegradable& biocompatible lipids & emulsifier is used for preparation of NLCs. NLCs have gained attention of researchers as an alternatives of SLN, polymeric nanoparticles, emulsions, microparticles, liposomes etc. the commonly used solid lipids & liquid lipids are oleic acid, capric triglyecrides , alpha tocopherols, soybean oil, cow ghee, black cumin oil, olive oil, sweet almond oil, squalene, stearic acid , glyceryl monostrearate, cetyl palmitate. The oral drug administration route provides a valuable option for treating various deadly diseases because of its several advantages like patient compliance, cost effectiveness and ease of administration and is regarded as the most commonly accepted route for drug administration. In this review what are NLC, its types , method of preparation discussed.

INTRODUCTION

Nanoparticles are defined as colloidal particulate systems having dimensions between 10-1000nm. NLCS are prepared from solid lipid, liquid lipid, surfactant, active ingredients & water.[1] Biodegradable & biocompatible lipids & emulsifier are used for preparation of NLCs.[2] NLCs have gained attention of researchers as an alternatives of SLN, polymeric nanoparticles, emulsions, microparticles, liposomes etc. the commonly used solid lipids & liquid lipids are oleic acid, capric triglycerides, alpha tocopherols, soybean oil, cow ghee, black cumin oil, olive oil, sweet almond oil, squalene, stearic acid , glyceryl monostrearate, cetyl palmitate.[3]

The oral drug administration route provides a valuable option for treating various deadly diseases because of its several advantages like patient compliance, cost effectiveness and ease of administration and is regarded as the most commonly accepted route for drug administration.[4] It is also highly preferred for chronically administered agents, such as anti-tumor, antidiabetic and antihypertensive agents, antipsychotic drugs, anti-inflammatory drugs.[5] Unfortunately, more than 40% of drugs coming out of the drug discovery and development processes are not suitable for oral delivery due to their hydrophobic nature and present poor oral bioavailability, that is, insufficient drug is presented to the site of action with subsequent lack of pharmacological action.[6] Several other barriers are also encountered with the oral route, which are responsible for comparatively poor plasma levels of orally administered drugs *viz.* poor permeability across the gastrointestinal membrane, first pass metabolism, drug expulsion via intestinal drug transporter, that is, P-glycoprotein (P-gp) and variability due to food effects [1,2,5-15], Therefore, there is a necessity for researchers to make advancements in oral drug delivery systems and the above mentioned factors need considerations for providing the desired therapeutic outcomes. [10,11,12,13,14,15]

For bioavailability enhancement, the researchers have attempted various approaches to overcome the challenges associated with oral delivery, such as Nano sizing of the drug molecules, salt formation, prodrug synthesis and encapsulation of drugs in nanosized carriers, such as polymeric micelles, nanoparticles, liposomes, emulsions, etc. [1,3,4.] NLCs possess unique characteristics and are formulated using a combination of solid and liquid lipids where less ordered structures are produced, which offer the firmer inclusion of the drug molecules within the matrix during the shelf life [16,17.] Also, the higher entrapment efficiency is due to higher solubility of drugs in liquid lipids in comparison to solid lipids[19]. Higher pay load

capacity along with long shelf storage stability thus makes NLCs as an advanced carrier in comparison to other conventional lipid-based systems. Further, NLCs have the feasibility of incorporating both hydrophilic and lipophilic drugs. In addition to this, they may provide sustained release of drugs and target them to the site of action. Various studies have proven that this nanoplatform has shown improvement in oral bioavailability of drugs via promoting their intestinal absorption [20.] This system has also shed a light of hope for treatment of chronic diseases due to its modulation with drug efficacy and sustained for longer periods.

Nanostructured lipid Carriers a Lipid-based (Drug Delivery System) DDS is a approach to manufacture pharmaceuticals for different dosage forms [21] Lipid formulations like Solid lipid nanoparticles (SLN) , Nanostructured lipid Carriers (NLC's)need a variety of the products to be incorporated in formulations. A variety of product includes mainly solid lipid, liquid lipid and a surfactant. The bioavailability and solubility of the insoluble drugs are two main criteria which can be enhances with the formulations like NLC's [22]. Still all major kind of parameters like choice of lipid, surfactants other essential excipients and methods of preparation varies which leads to change in parameters like particle shape and size, phase transition, solubility, bioavailability of drug etc. Though Many pharmaceutical companies have developed a well-established industrial process for the manufacturing of large-scale batches of nanostructured lipid carriers [22,23].

Lipid nano formulations make dispersions of fairly water-soluble drugs and can decrease the characteristic restrictions of slow and imperfect dissolution of fairly water-soluble drugs like Biopharmaceutics Classification System (BCS) class II and simplify the formation of solubilized phases from which drug absorption occurs easily. In any, another vehicle mediated delivery system like an emulsion, liposome the degree and mode of drug release from the system are important in relation to the movement of the delivery system *in-vivo* [25,27].

A lipid matrix is available inside the newly made NLC's having a very special nanostructure which was developed by Muller [23,28]. This special type of NLC's nanostructure also helps to increase bioavailability, drug loading and solubility of the drug in different conditions and environments [29.] There are multiple techniques and methods by which means this kind of NLC's can be prepared or formulated like high-pressure homogenization. As per the literature near about 30-80 percent of the product yield can be obtained by these methods after adjusting the different conations and environments [30].

The first time NLC's was introduced in 1990s as another carrier system [32]. The solid lipid carrier systems which are available in nanometer range like solid lipid nanoparticles (SLN), was presented as a substitute to liposomes. But there are multiple limitations related with SLN, such as incomplete drug loading ability and drug expulsion thru storage, all these limitations can be minimized or waived off by newer solid lipids DDS like NLC's. There is new and modified type of NLC's are available which is having a meticulous nanostructure. These meticulous nanostructures are responsible and also help to improve the stability of the formulations as well as increase the bioavailability, drug loading [29]. NLC's also minimized the different problems which are associated with the SLN for many drugs, problems like low payload, drug expulsion during storage and SLN's dispersions due to the high-water content in it [32-35].

Structure of NLC's

The structure of NLS's are very and somehow similar to SLNs, NLCs have three very specific features [24]. These properties are based up on the location the drug is going to be integrated [32,34,35] three different methods were adopted for a development and formulation of nanostructure NLCs.

- NLC type I also called as imperfect crystal.
- NLC type II also called as multiple type.
- NLC type III also called as amorphous type as shown in Figure [36]

NLC type I

NLC type I also called imperfect crystal types have a badly structured solid matrix. The different fatty acids such as glycerides can be used to improve and modify the structure. The total number of imperfections in the structure are responsible and also helpful for the property of good drug which can be easily increased [24]. The type I of NLC's can be prepared by mixing spatially different lipids which can leads to imperfections in the crystal lattice. The drug molecules lodges extra disorderly crystal as molecular form and amorphous clusters. To avoid this adding to a minor quantity of liquid lipid additional leans to increases the drug-loading. The small quality of the glycerides can be used to overcome this situation [24].

It was well documented in literature that If there is the change in the structure of the lipids,

the problems like cluster of drugs arise and leads to disorderly imperfect lipid matrix and all this occurs is due to crystallization method [24].

NLC type II

The oil-in-lipid-in-water type is II type of NLC's also called as multiple type. In type II NLC's, the solubility of oil is greater as compare to solubility of solid lipids. In type II NLC's high amount of oil are mixed with solid lipids due to this oil molecule can effortlessly spread into the lipid matrix at a low concentration of oil [24,37,38]. If the added oil in excess quantity than required of its solubility can lead to separation of different phases, finally produces small oily nano compartments which are bounded by the solid lipid matrix [28,33,39.]

This kind of formulation permit controlled drug release and leakage of drug from lipid matrix 34. In this case, lipophilic drugs can be made soluble in oil first and type II method can be followed with the cooling procedure of a hot homogenization process [24,40,41].

NLC type III

The III type of NLS's also called as amorphous type. In this technique of prepration of NLC's, the lipids are mixed in such a way that crystallizing can be prevented through mixing procedure. In type III method the lipid matrix remains solid but, in an amorphous state. The technique and method of crystallization often leads to drug expulsion. To minimize this, NLCs can also be formulated by carefully mixing of solid lipids with special lipids such as hydroxy octacosanyl hydroxyl stearate, isopropyl palmitate or MCT. Solid, but non-crystalline NLC are formed [24,42,43].

Component of the NLC Lipids

The lipid, itself, is the main ingredient of NLC that influence their drug loading capacity, their stability and the sustained release behavior of the formulations [24]. Lipid nanoparticle dispersions are based upon a variety of lipid materials including fatty acids, glycerides, and waxes. Most of these lipids, with the notable exception of cetyl palmitate, are approved as generally-recognised-as-safe (GRAS) and are physiologically well-tolerated [24]. Selection of appropriate lipids is essential prior to their use in preparation of lipid nanoparticle dispersions [24]. Although there are no specific guidelines, empirical values, such as the solubility of drug in the lipid have been proposed as suitable criteria for selection of an appropriate lipid

crystallization in lipids with longer chains of fatty acids are slower than those with shorter fatty acid chains. Wax-based NLC physically more stable, however, they exhibit significant drug expulsion cause of their more crystalline nature 22,24,44. To avoid such problems with lipid crystallinity and polymorphism, a binary mixture of two spatially different solid lipid matrices, i.e., a solid lipid and a liquid lipid (or oil) was used to prepare lipid nanoparticle dispersions, now known as nanostructured lipid carriers (NLC) [45,46].

Solid lipids

A combination of numerous chemical compounds which have a melting point higher than 40°C.

These solid lipids are well tolerated [47-49].

- Accepted for human use.
- Also *in-vivo* biodegradable.

Examples are beeswax, carnauba wax, dynasan, precifac, stearic acid, ppifil, cutina CP 8 etc.

Liquid lipids (oil)

These liquid lipids are well tolerated and accepted for human use. Examples are Cetiol V, miglyol, castor oil, oleic acid, davana oil, palm oil, olive oil etc. [47-49] as shown in Table 2.

Table 2: Lipids used in the preparation of nanostructured lipid carriers [23,24].

Emulsifying agents – surfactants

Surfactants are the compounds which are adsorbed at interfaces and reduce the interfacial tension. When a surfactant is present in small amounts, it improves the stability by decreasing the rates of surfactants also termed as surface-active agents [23,24,50]. At low concentrations, surfactants adsorb onto the surface of a system or interface. Surfactant decreases the surface or interfacial free energy and decrease the surface or interfacial tension between the two phases [22,24,41].

The categories and type of surfactants are mentioned in Table 3[24]. The selection of surfactants for NLCs based upon a number of multiple factors, like route of administration of

NLCs, HLB value of surfactant [24,51]. The surfactants and co-surfactants are given in Table. [24,52-54].

Table 1: Classification of surfactants and co-surfactants for the preparation of NLC's 24,55.

Surfactants	
Ionic surfactants	Non-ionic surfactants
Sodium taurodeoxycholate, Sodium oleate, Sodium dodecyl sulphure	**Span 20, 80, 85, Tween 20, 80, Tyloxapol, Poloxamer 188 Poloxamer 407, Solutol HS15**
Amphoteric surfactants	Co-surfactants
Egg phospholipid (Lipoid E 80, Lipoid E 80 S) Soy	**Butanol, Butyric acid**
Hydrogenated soy phosphatidylcholine (Lipoid S PC-3,	
Hydrogenated egg phosphatidylcholine (Lipoid E PC-3)	
Phospholipon 80 H, Phospholipon 90 H)	

.The combination of solid and liquid- lipid mixtures will not help much for the doing the perfect crystallization in case if formulation of NLC's. To overcome this problem reducing the probability of expulsion of the encapsulated drug upon storage [24,28,56]. The addition of polysorbate 80 possibly provided more interfacial area than polysorbate 20 [24]. As a result, the average size of NLC's 80 was smaller than NLC's 20. The properties of NLCs can be influenced by the type of surfactant used in the formulation [26]. The type of stabilizer significantly affected the average size and charge but not the size distribution of the NLCs [24,57].NLCs have excellent features and properties that can rise the presentation of a variability of integrated drug forms [24]. The properties of the NLCs are really influenced by the type of surfactant used [24].

The Effect of surfactant concentration on the particle size and particle size distribution of NLC [24]. NLC can be stable by creating electrostatic and steric repulsion between particles. Some properties of both electrostatic and steric repulsion are mentioned. The steric interaction is dependent on the separation distance between the internal aqueous droplets and

the external aqueous phase, the thicknesses of the two adsorbed surfactant layers, the size of the internal aqueous droplets and the oil globules, all of which determine the extent of the compression of the adsorbed surfactant molecules [26]. The thickness of each of the two surfactant layers have the same effect on the steric repulsion, and stronger steric interaction can be achieved with thicker adsorbed layers, which can effectively prevent coalescence between the internal aqueous droplets and the external aqueous phase. Increasing the internal aqueous droplet size can produce stronger steric repulsion; however, larger oil globules will weaken the steric repulsion, indicating that a more stable double- emulsion system can be achieved by preparing the system with smaller oil globules and larger internal aqueous droplets [26] Polyhydroxy surfactants stabilize systems by creating spatial exclusion and due to their non-ionic nature, low and zero zeta potential would be obtained stated that the stability of nano lipid carrier against aggregation is influenced by the ionic strength of the continuous phase and the charge density on the surface of the water and fat. High zeta potential along with the non-electrostatic agents such as steric forces has also an important impact on the stability The agents used in the preparation of nanostructured lipid carriers are shown in Table 3 [26].

Methods of preparation of NLS's

There are several methods are developed for the preparation of NLS's [26]. The most command methods are as follows:

- High-pressure homogenization (HPH)
- Solvent emulsification evaporation method
- Solvent emulsification diffusion method
- Solvent injection method
- Microemulsion method
- Double emulsion technique
- Ultrasonication or high-speed homogenization
- Phase inversion method

- Membrane contractor technique
- Supercritical fluid (SCF) method
- Hot-melt extrusion (HME) technology

High-pressure homogenization

In this process a stable emulsion can be made which involves the subdivision particles into nanosize. In the market, two types of homogenizers are available a) jet-stream homogenizers b) piston-gap homogenizers. There are three methods predominantly used to prepare NLCs by High-pressure homogenization are as follows and shown in Figure 1[26].

- Hot homogenization
- Cold homogenization
- Microemulsion

The hot homogenization process is executed always at temperature above the melting point of the lipids used in the formulation. While in cold homogenization method the lipid melt is cooled and the solid lipid is ground to lipid micro particles. [26]

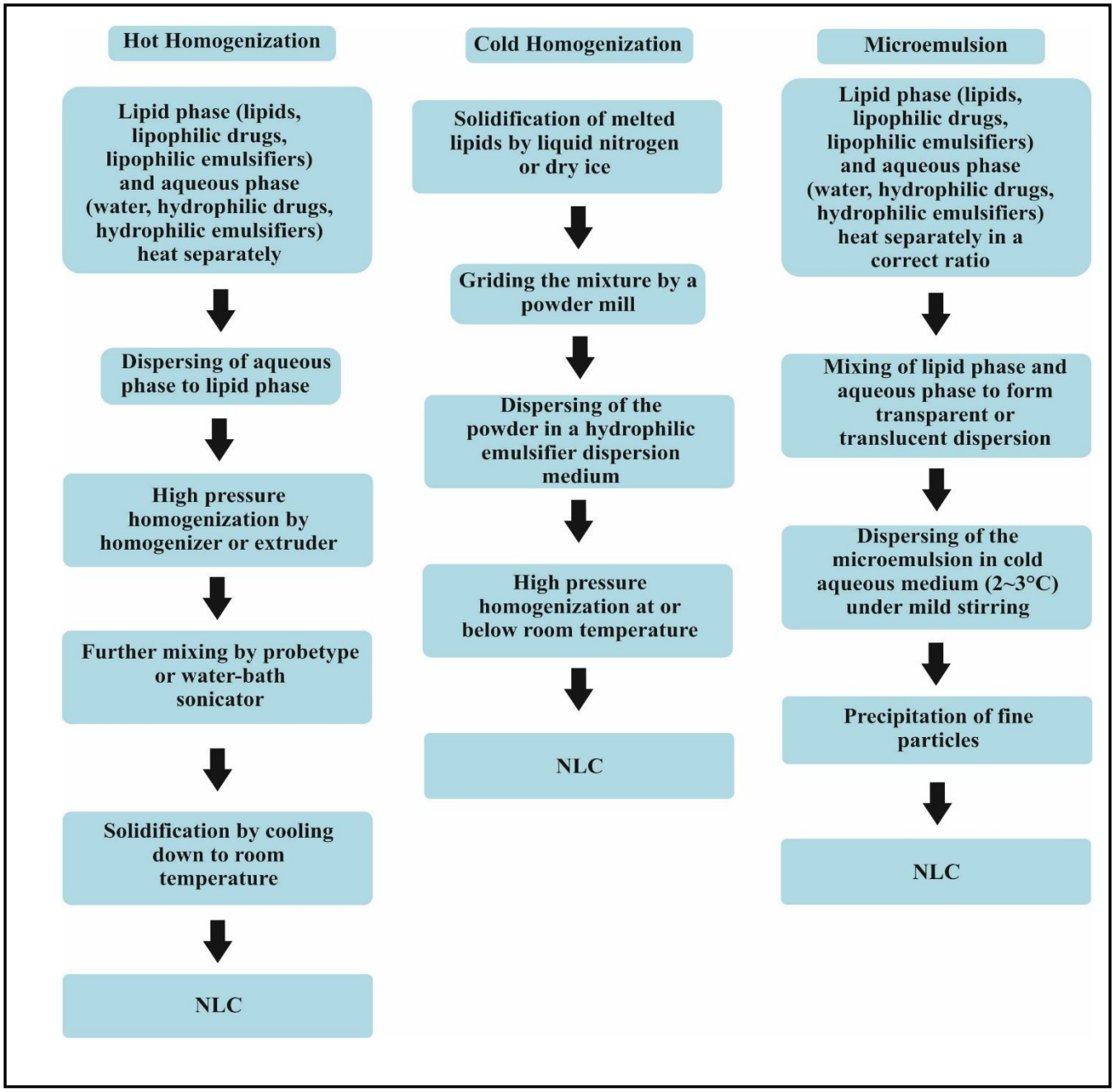

Figure No. 1

Solvent emulsification evaporation method

This method can be employed for sizes ranging from 30 to 100 nm depending upon the types of lipids and surfactants used [58]. In this process, the drug accompanying the lipids is added to organic solvent (water-immiscible) and emulsified with an aqueous solution of surfactant to form an o/w emulsion. The organic solvent is then removed by evaporation at low pressure that eventually forms NLCs due to lipid precipitation by aqueous media on evaporation of the organic solvent (Fig. 2) [59]. This method is ideal for heat-sensitive medicines since it is devoid

of thermal stresses. The most significant limitation of this process is the usage of organic solvents, as sometimes residues of organic solvents remain in the final product, which may produce toxic effects after administration [60]. It was also reported that homogenization effectiveness gets reduced with an increase in the lipid concentration, resulting in highly dilute dispersions with very low lipid particle contents [61].

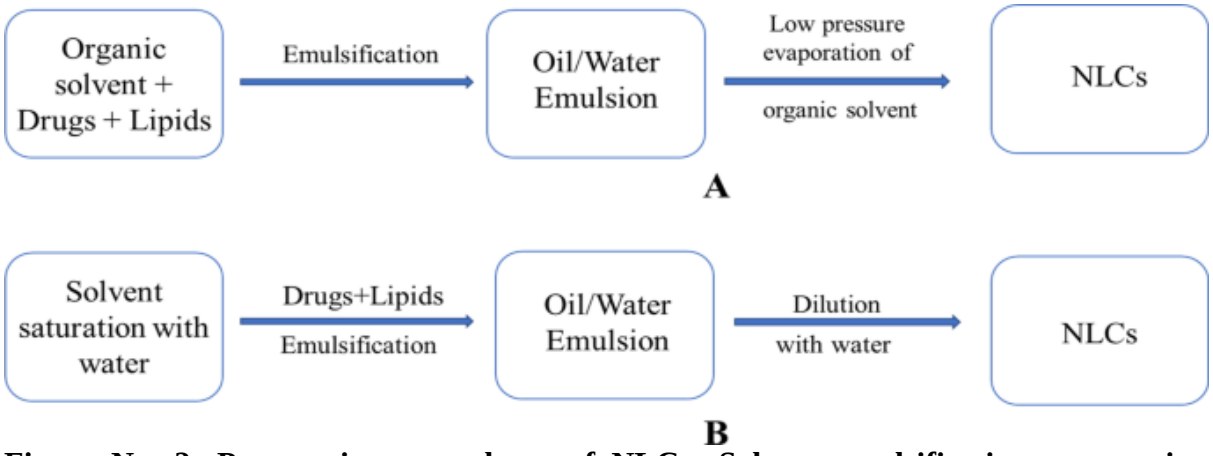

Figure No. 2: Preparation procedures of NLCs: Solvent emulsification evaporation method

Solvent emulsification diffusion method

This method uses partly water-miscible solvents (such as ethanol, benzyl alcohol, tetrahydrofuran) as a means of dispersing the lipids and the drugs [62]. This process begins with the mutual saturation of the solvent and water so as to maintain the thermodynamic equilibrium. Afterwards, API and lipids are added and emulsified to form an o/w emulsion. The emulsion is then diluted with water in a ratio varying from 1:5 to 1:10 to allow solvent diffusion into a continuous phase, thus precipitating the nanoparticles (Fig. 2.) The excess solvent can be removed by either lyophilization or ultrafiltration after the precipitation of NLCs [62,63].

Solvent injection method

This technique is also known as the solvent displacement method. It works on the principle of quick diffusion of solvent over lipids interfaced with an aqueous solvent. In this method, both the solid and liquid lipids are added to water-miscible solvent (alcohols like ethanol, isopropyl alcohol) or a mixture of water-miscible solvents and speedily injected into the surfactant solution with continuous stirring. As a result, the lipid nanoparticles get precipitated in the aqueous solution as the solvent migrates quickly through it [64]

This method is versatile and has a faster production rate, low shear stress, and high efficiency without using sophisticated equipment like a high-pressure homogenizer. However, particle size can be a concern with lipophilic solvents as more lipophilic solvents produce larger particles. The possibility of organic solvent residues can be another issue with this method [61,65].

Microemulsion method

It is a popular method used for both polar and non-polar drugs. It involves the addition of melted lipids to an aqueous solution of the drug along with a surfactant and co-surfactant to form an emulsion, the nature of which depends upon the ratios of hydrophilic and lipophilic phase used. The resulted emulsion is dispersed in chilled water in a ratio from 1:25 to 1:50 under mild agitation, ultimately giving NLC dispersion (Fig.) [66,67,68].Even though this method is simple, time-saving and can be used for thermolabile substances, it is associated with various limitations like usage of large volumes of water for dilution and requires an appreciable quantity of surfactants for formulation [69,70].

Figure No. 3: Preparation procedures of NLCs: Microemulsion Method

Double emulsion technique

This method is extensively employed for hydrophilic drugs as well as for thermosensitive drugs [71]In this approach, a hydrophilic drug in aqueous media is emulsified in lipid melt, with lipophilic surfactants to form w/o emulsion. The primary emulsion is then added to an aqueous solution of hydrophilic solvent to form w/o/w emulsion (double emulsion); thereupon, the NLCs are purified from the dispersion by solvent evaporation and ultrafiltration [72,73]. Although this method is simple, requires a modest energy input and there is no need for sophisticated instruments, it is only suitable for systems with a low lipid content [73].

Ultrasonication or high-speed homogenization

This method works on the principle of cavitation and is one of the least studied techniques. Firstly, the lipids are melted, and the active drug is added to them. This melt is added to the surfactant solution previously heated to the same temperature, followed by emulsification using a high-speed stirrer. The obtained pre-emulsion is further ultrasonicated with the help of a probe ultrasonicator. The dispersion is cooled to get the lipid nanoparticles [74,75,76] This technique saves both time and energy, but NLCs obtained from ultrasonication suffer from several shortcomings like contamination by metals, clumping of particles on storage, and low stability of NLCs [77,78,79].

Phase inversion temperature method

As the name suggests, this technique is based on the principle of temperature-induced phase inversion of an emulsion. In this process, non-ionic polyoxyethylated surfactants are used whose properties are dependent on the temperature. At low temperatures, the hydrophilic–lipophilic balance (HLB) value of these surfactants is high because of the hydration of the hydrophilic groups. But as the temperature increases, their HLB value starts to decrease because of the dehydration of the ethoxy groups. There is a point (temperature) where the surfactant molecule has an equal affinity towards both lipophilic and hydrophilic phases, and this temperature is known as phase inversion temperature [80,81,82] When the temperature is above the phase inversion temperature, w/o-type emulsion is formed and vice versa 83 The lipids, oils, water, and surfactants are mixed and heated above the phase inversion temperature, followed by stirring using a magnetic stirrer to form a w/o emulsion. Subsequently, three cycles of heating and cooling (85 °C–60°C–85 °C) are applied at a rate of 4 °C/min. This hot mixture is then diluted with cold water to allow phase inversion (from w/o emulsion to o/w emulsion) and leads to the formation of NLCs [82,83] This is a novel method offering the advantage of incorporating thermolabile drugs without using any organic solvent [84,85].

Membrane contractor method

It is a relatively recent approach for the production of NLCs. The procedure involves heating the lipid phase to a temperature over its melting point in a pressured tank. The liquid is then passed down a tube and pushed against membrane pores, resulting in the production of tiny droplets. The aqueous phase sweeps away any droplets accumulating at the pore outputs as it

circulates inside the membrane module. The dispersion so obtained is cooled to precipitate the NLCs. The particle size is determined by the temperature of the lipid and aqueous phases, the membrane aperture size, and the lipid phase pressure. The advantages of this technique include the ability to regulate particle size by varying the process parameters and the simplicity of scale-up [86,87]. However, clogging of the membrane is the only problem with this procedure [88].

Supercritical fluid (SCF) method

A wide range of applications, such as extraction, green chemical reactions, and chromatography, have made use of supercritical fluids. Recently, this technology has been explored for the formation of micro- and nanoparticles. However, the use of supercritical fluid technology in particle production is still in its early stages of development.

A supercritical fluid is a liquid or gas that can coexist at temperatures and pressures above the critical temperature and critical pressure. It has characteristics that are distinct from those of gases or liquids under normal circumstances [89] Supercritical carbon dioxide is one of the widely used SCFs owing to its abundance, inertness, non-flammable, and easily attainable critical conditions ($T_c = \sim 31$ °C and $P_c = 73.8$ bar) [90]Generally, the solid lipids are melted and added to SCF along with the drug and liquid lipids to solubilize them. Either a gas-saturated suspension or a solution is formed depending on the components' solubility in the SCF. Afterwards, the resultant dispersion is atomized and is sprayed in an enclosed chamber, where the decompression and evaporation of the gas lead to the formation of nanostructured lipid carriers [91] Chattopadhyay et al. employed a different technique (SCF extraction of emulsions) for preparing NLCs using SCF. The research group formed an o/w emulsion, which was added to the extraction column and extracted using supercritical carbon dioxide. There is a rapid and complete removal of the solvent, resulting in the precipitation of NLCs. In addition, it was reported that the NLCs formed had a uniform particle size [92].

SCF method offers numerous benefits, including the avoidance of organic solvents and the production of dry powder particles rather than suspensions. Also, as the density of SCFs fluctuates with pressure, a simple depressurization process with pressure adjustments may be used to separate and recover the solvent [93].

Hot-melt extrusion (HME) technology

It is one of the most widely used processing techniques in the plastic industry. Earlier, the HME method was used for manufacturing tubes, plastic bags, and pipes. However, since the 1980s, there has been a rising interest in the use of HME in the pharmaceutical industry and has now been used for manufacturing tablets, capsules, implants, etc. [94] This method involves pumping the APIs and excipients with a heated rotating screw (extruder) at a higher pressure and is passed through a die to form uniform-sized nanoparticles. An emulsion is formed when the APIs and excipients are passed through an extruder, and afterwards, the size of the obtained emulsion is reduced by passing through the die [95,96].

HME method has several advantages, such as no solvents are used in this method; hence, there is no need for the drying process. Also, it is used for enhancing the solubility and bioavailability of hydrophobic drugs. Furthermore, it is a cost-effective method that involves a shorter manufacturing time, fewer stages, and continuous operation. HME is chosen over other fusion processes because the mixture's residence time in the extruder is short, preventing deterioration of heat-sensitive components [95,97] HME, on the other hand, is performed at high temperatures that cannot be used to formulate thermolabile compounds. HME requires excipients with high flow properties. Additionally, the equipment is relatively expensive, and the driving unit requires a significant amount of energy. However, the majority of these drawbacks may be mitigated by adjusting process parameters appropriately [95,97,98].

CONCLUSION:

Nanostructured lipid carriers have proved to be a promising drug delivery vehicle for enhancing oral bioavailability. Having the benefits of other nanocarriers like liposomes, SLNs and by circumventing some of their drawbacks, NLCs have become a center of attraction for scientists. NLCs as drug carriers offer a high drug loading capacity for drug distribution through a variety of routes, including oral, parenteral, nasal, topical, ophthalmic, and pulmonary routes, while improving the physical and chemical stability of the medications, providing versatile release regulation, shielding them from degradation, and provide improved biopharmaceutical attributes.

REFERENCES

1. Pathak K, Raghuvanshi S. Oral bioavailability: issues and solutions via nanoformulations. Clin. Pharmacokinet. 2015;54(4):325–357. [PubMed] [Google Scholar]
2. Desai PP, Date AA, Patravale VB. Overcoming poor oral bioavailability using nanoparticle formulations – opportunities and limitations. Drug Discov. Today Technol. 2012;9(2):87–95. [PubMed] [Google Scholar]
3.Savjani KT, Gajjar AK, Savjani JK. Drug solubility: importance and enhancement techniques. ISRN Pharm. 2012;2012:1–10. [PMC free article] [PubMed] [Google Scholar]
4.Silva AC, Santos D, Ferreira D, et al. Lipid-based nanocarriers as an alternative for oral delivery of poorly water-soluble drugs: peroral and mucosal routes. Curr. Med. Chem. 2012;19(26):4495–4510. [PubMed] [Google Scholar]
5. Shaji J, Patole V. Protein and peptide drug delivery: oral approaches. Indian J. Pharm. Sci. 2008;70(3):269–277. [PMC free article] [PubMed] [Google Scholar]
6. Peng SX, Ritchie DM, Cousineau M, et al. Altered oral bioavailability and pharmacokinetics of P-glycoprotein substrates by coadministration of biochanin A. J. Pharm. Sci. 2006;95(9):1984–1993. [PubMed] [Google Scholar]
7. Amin ML. P-glycoprotein inhibition for optimal drug delivery. Drug Target Insights. 2013;7:27–34. [PMC free article] [PubMed] [Google Scholar]
8. Managuli, R.S., Wang, J.T., Faruqu, F.N., Kushwah, V., Raut, S.Y., Shreya, A.B., Al-Jamal, K.T., Jain, S., Mutalik, S., 2019. Asenapine maleate-loaded nanostructured lipid carriers: optimization and in vitro, ex vivo and in vivo evaluations. Nanomedicine (Lond.). 14 (7), 889- 910. https://doi.org/10.2217/nnm-2018-0289.
9. Jawahar, N., Hingarh, P.K., Arun, R., Selvaraj, J., Anbarasan, A., S, S., G, N., 2018. Enhanced oral bioavailability of an antipsychotic drug through nanostructured lipid carriers. Int. J. Biol. Macromol. 110, 269-275. http://doi.org/10.1016/j.ijbiomac.2018.01.121.
10. Khan, S., Shaharyar, M., Fazil, M., Baboota, S., Ali, J., 2016a. Tacrolimus-loaded nanostructured lipid carriers for oral delivery - Optimization of production and characterization. Eur. J. Pharm. Biopharm. 108, 277-288. https://doi.org/10.1016/j.ejpb.2016.07.017.
11. Luan, J., Zheng, F., Yang, X., Yu, A., Zhai, G., 2015. Nanostructured lipid carriers for oral delivery of baicalin: In vitro and in vivo evaluation. Colloids Surf. A Physicochem. Eng. Asp. 466, 154-159. https://doi.org/10.1016/j.colsurfa.2014.11.015.
12. Tran, T.H., Ramasamy, T., Truong, D.H., Choi, H., Yong, C.S., Kim, J.O., 2014. Preparation and characterization of fenofibrate-loaded nanostructured lipid carriers for oral bioavailability enhancement. AAPS PharmSciTech. 15 (6), 1509-1515. https://doi.org/10.1208/s12249-014- 0175-y.
13. Ranpise, N.S., Korabu, S.S., Ghodake, V.N., 2014. Second generation lipid nanoparticles (NLC) as an oral drug carrier for delivery of lercanidipine hydrochloride. Colloids Surf B Biointerfaces. 116, 81-87. https://doi.org/10.1016/j.colsurfb.2013.12.012.
14. Beloqui, A., delPozo-Rodríguez, A., Isla, A., Rodríguez-Gascón, A., Solinísb, M.A., 2017. Nanostructured lipid carriers as oral delivery systems for poorly soluble drugs. J. Drug Deliv. Sci. Technol. 42, 144-154. http://doi.org/10.1016/j.jddst.2017.06.013.
15. NeelamPoonia, [1] Rajeev Kharb, [2] Viney Lather, [3] and DeeptiPandita[*] [1]Nanostructured lipid carriers: versatile oral delivery vehicle doi: 10.4155/fsoa-2016-0030fsg
16. Khan S, Baboota S, Ali J, et al. Nanostructured lipid carriers: an emerging platform for improving oral bioavailability of lipophilic drugs. Int. J. Pharm. Investig. 2015;5(4):182–191. [PMC free article] [PubMed] [Google Scholar]
17. Chaudhary S, Garg T, Murthy RS, et al. Development, optimization and evaluation of long chain nanolipid carrier for hepatic delivery of silymarin through lymphatic transport pathway. Int. J. Pharm. 2015;485(1–2):108–121. [PubMed] [Google Scholar]
18. Iqbal MA, Md S, Sahni JK, et al. Nanostructured lipid carriers system: recent advances in drug delivery. J. Drug Target. 2012;20(10):813–830. [PubMed] [Google Scholar]
19. Muchow M, Maincent P, Muller RH. Lipid nanoparticles with a solid matrix (SLN, NLC, LDC) for oral drug delivery. Drug Dev. Ind. Pharm. 2008;34(12):1394–1405. [PubMed] [Google Scholar]

20. Tamjidi F, Shahedi M, Varshosaz J, et al. Nanostructured lipid carriers (NLC): a potential delivery system for bioactive food molecules. Innov. Food Sci. Emerg. Technol. 2013;19:29–43. [Google Scholar]

21 June IM, Davange RM, Salunkhe KS, Chaudhari SR, Deshmukh PD, et al. (2016) Nanostructured lipid carrier: Novel drug delivery system. J Adv Drug Deliv 3: 7-16.

22. Xia Q, Wang H (2010) Preparation and characterization of coenzymes Q-10 loaded NLC. NSTI-Nanotech 3: 498-501.

23.Nair R, Kumar KSA, Priya KV, Sevukarajan M (2011) Recent advances in solid lipid nanoparticle based drug delivery systems. J Biomed Sci Res 3: 368-84.

24.Shah R, Eldridge D, Palombo E, Harding I (2015) Lipid Nanoparticles: Production, Characterization and Stability. Briefs Pharm Sci Drug Dev 1: 11-23.

25.Jaiswal P, Gidwani B, Vyas A (2016) Nanostructured lipid carriers and their current application in targeted drug delivery. Artif Cells Nanomed

26. Sharma A, Baldi A (2018) Nanostructured Lipid Carriers: A Review. J Develop Drugs 7: 191. doi:10.4172/2329-6631.1000191

27. Müller R (2000) Solid lipid nanoparticles (SLN) for controlled drug delivery: a review of the state of the art. Eur J Pharm Biopharm 50: 161-177.

28.Radtke M, Müller RH (1991) Nanostructured Lipid Carriers: A novel generation of solid lipid drug drug Carriers. Pharmaceutical Technology Europe 17: 1-4.

29 Peddinti S (2016) Nanostructured lipid carriers as a drug carrier. J Pharm Nanotechnol Nanostruc 4: 68-74.

30 Dubey A, Prabhu P, Kamath JV (2012) Nano structured lipid carriers: A novel topical drug delivery system. Int J PharmTech Res 4: 705-714.

31 Purohit DK, Nandgude TD, Poddar SS (2016) Nano-lipid carriers for topical application: Current scenario. Asian J Pharm 10: 1-9.

32 Jenning V, Gysler A, Schäfer-Korting M, Gohla S (2000) Vitamin A loaded solid lipid nanoparticles for topical use: occlusive properties and drug targeting to the upper skin. Pharm Biopharm 49: 211-218.

33 Jenning V, Schafer-Korting M, Gohla S (2000) Vitamin A-loaded solid lipid nanoparticles for topical use: drug release properties. J Control Release 66: 115-126.

34 Jenning V, Mäder KGS (2000) Solid lipid nanoparticles (SLNTM) based on binary mixtures of liquid and solid lipids: a 1H-NMR study. Pharm 205: 15-21.

35 Jenning V, Gohla S (2000) Comparison of wax and glyceride solid lipid nanoparticles. Int J Pharm Sci 196: 219-222

36 Lopes CPA (2014) Development and Characterization of Lipid Nanoparticles prepared by Miniemulsion Technique.

37 Radtke M, Muller R (2001) Nanostructured lipid drug carriers. New Drugs 48-52.

38 Zhang H, Dang Q, Zhang Z, Wu F (2017) Development, characterization and evaluation of doxorubicin nanostructured lipid carriers for prostate cancer. JBUON 22: 102-11.

39 Zhang H, Dang Q, Zhang Z, Wu F (2017) Development, characterization and evaluation of doxorubicin nanostructured lipid carriers for prostate cancer. JBUON 22: 102-11.

40 Arunkumar N, Deecaraman M, Rani C (2014) Nanosuspension technology and its applications in drug delivery. Asian J Pharm 3: 168.

41 Persson LC, Porter CJH, Charman WN, Bergström CAS (2013) Computational prediction of drug solubility in lipid based formulation excipients. Pharm Res 30: 3225-3237.

42 Karunakar G, Patel NP, Kamal SS (2016) Nano structured lipid carrier based drug delivery system. J Chem Pharm Res 8: 627-643.

43 Soni K, Kukereja BK, Kapur M, Kohli K (2015) Lipid nanoparticles: future of oral drug delivery and their current trends and regulatory issues. Int J Curr Pharm Rev Res 7: 1-18.

44 Mottalib A, Kasetty M, Mar JY, Elseaidy T, Ashrafzadeh S, et al. (2017) Weight Management in Patients with Type 1 Diabetes and Obesity. Curr Diab Rep 17: 92.

45 Gaba B, Fazil M, Khan S, Ali A, Baboota S, et al. (2015) Nanostructured lipid carrier system for topical delivery of terbinafine hydrochloride. Bull Fac Pharmacy 53: 147-159.

46 Fang CL, Al-Suwayeh SA, Fang JY (2012) Nanostructured Lipid Carriers (NLCs) for Drug Delivery and Targeting. Recent Pat Nanotechnol 7: 41-55.

47 Upreti T (2017) Nanostructured Lipid Carrier System for the Treatment for Skin Disease-A Review. JSM Nanotechnol Nanomedicine 5: 1059.

48 Chen PC, Huang JW, Pang J (2013) An investigation of optimum NLC- sunscreen formulation using taguchi analysis. J Nanomater pp: 1-11.

49 Joshi M, Patravale V (2006) Formulation and Evaluation of Nanostructured Lipid Carrier (NLC)–based Gel of Valdecoxib. Drug Dev Ind Pharm 32: 911-918.

50 Joshi M, Pathak S, Sharma S, Patravale V (2008) Design and in vivo pharmacodynamic evaluation of nanostructured lipid carriers for parenteral delivery of artemether: Nanoject. Int J Pharm 364: 119-26.

51 Lasoń E, Sikora E, Ogonowski J (2013) Influence of process parameters on properties of Nanostructured Lipid Carriers (NLC) formulation. Acta Biochem Pol 60: 773-777.

52 Ekambaram P, Sathalia AH, Priyanka K (2012) Solid Lipid Nanoparticles: A Review. Sci Rev Chem Commun 2: 80-102.

53 Doktorovova S (2009) Lipid nanoparticle mediated drug delivery for safer cancer treatment: example of paclitaxel. Rev da Fac Ciências da Saúde 6: 84-93.

54 Patron C, Convener W (2017) Workshop on research methodology and data analysis through SPSS.

55 Gaba B, Fazil M, Khan S, Ali A, Baboota S, et al. (2015) Nanostructured lipid carrier system for topical delivery of terbinafine hydrochloride. Bull Fac Pharmacy 53: 147-159.

56 Uner M, Yener G (2007) Importance of solid lipid nanoparticles (SLN) in various administration routes and future perspective. Int J Nano medicine 2: 289-300

57 Sabtua R, Hasham R, Roslic NA, Azizd AA, Azize R (2015) Akademia baru effect of high pressure homogenizer on the formation of zingiber officinale- loaded nanostructured lipid carrier. J Adv Res Mater Sci 13: 16-21.

58 Mehnert W, Mäder K (2012) Solid lipid nanoparticles: production, characterization and applications. Adv Drug Deliv Rev 64:83–101. https://doi.org/10.1016/J.ADDR.2012.09.021

59 Kumar R (2019) Lipid-based nanoparticles for drug-delivery systems. In: Mohapatra SS, Ranjan S, Dasgupta N et al (eds) Nanocarriers for drug delivery. Elsevier, pp 249–284

60 Salvi VR, Pawar P (2019) Nanostructured lipid carriers (NLC) system: a novel drug targeting carrier. J Drug Deliv Sci Technol 51:255–267. https://doi.org/10.1016/J.JDDST.2019.02.017

61 Shah MR, Imran M, Ullah S (2017) Solid lipid nanoparticles. Lipid-based nanocarriers for drug delivery and diagnosis. William Andrew Publishing, pp 1–35

62 Svilenov H, Tzachev C (2014) Solid lipid nanoparticles-a promising drug delivery system. In: Seifalian A, de Mel A, Kalaskar DM (eds) Nanomedicine. One Central Press, pp 187–237

63 Ganesan P, Narayanasamy D (2017) Lipid nanoparticles: Different preparation techniques, characterization, hurdles, and strategies for the production of solid lipid nanoparticles and nanostructured lipid carriers for oral drug delivery. Sustain Chem Pharm 6:37–56. https://doi.org/10.1016/J.SCP.2017.07.002

64 Schubert MA, Müller-Goymann CC (2003) Solvent injection as a new approach for manufacturing lipid nanoparticles—evaluation of the method and process parameters. Eur J Pharm Biopharm 55:125–131. https://doi.org/10.1016/S0939-6411(02)00130-3

65 Amandeep BS, Kumar M et al (2020) Recent advances in the development of the nanostructured lipid carriers for the topical fungal infections. J Reports Pharm Sci 9:271. https://doi.org/10.4103/jrptps.JRPTPS_99_19

66 Bornare AS, Saudagar RB (2017) Nanostructured lipid carrier (NLC): a modern approach for transdermal drug delivery. Res J Pharm Technol 10:2784–2792. https://doi.org/10.5958/0974-360X.2017.00493.0

67 Kotmakçı M, Akbaba H, Erel G et al (2016) Improved method for solid lipid nanoparticle preparation based on hot microemulsions: preparation, characterization, cytotoxicity, and hemocompatibility evaluation. AAPS PharmSciTech 18:1355–1365. https://doi.org/10.1208/S12249-016-0606-Z

68 Xia Q, Hao X, Lu Y et al (2008) Production of drug-loaded lipid nanoparticles based on phase behaviors of special hot microemulsions. Colloids Surfaces A Physicochem Eng Asp 313–314:27–30. https://doi.org/10.1016/J.COLSURFA.2007.04.067
69 Hanumanaik M, Patel SK, Sree KR (2013) Solid lipid nanoparticles; a review. Int J Pharm Sci Res 4:928–940. https://doi.org/10.13040/IJPSR.0975-8232.4(3).928-40
70 Surender V, Deepika M (2016) Solid lipid nanoparticles: a comprehensive review. J Chem Pharm Res 8:102–114
71 Iqbal M, Zafar N, Fessi H, Elaissari A (2015) Double emulsion solvent evaporation techniques used for drug encapsulation. Int J Pharm 496:173–190. https://doi.org/10.1016/J.IJPHARM.2015.10.057
72 Kanojia N, Sharma N, Gupta N, Singh S (2021) Applications of nanostructured lipid carriers: recent advancements and patent review. Biointerface Res Appl Chem 12:638–652. https://doi.org/10.33263/BRIAC121.638652
73 Rawal SU, Patel MM (2018) Lipid nanoparticulate systems: modern versatile drug carriers. In: Grumezescu AM (ed) Lipid nanocarriers for drug targeting. William Andrew Publishing, pp 49–138
74 Li Q, Cai T, Huang Y et al (2017) A review of the structure, preparation, and application of NLCs, PNPs, and PLNs. Nanomaterials 7:122. https://doi.org/10.3390/nano7060122
75 Reddy SH, Umashankar MS, Damodharan N (2018) Formulation, characterization and applications on solid lipid nanoparticles—a review. Res J Pharm Technol 11:5691–5700. https://doi.org/10.5958/0974-360X.2018.01031.4
76 Das S, Chaudhury A (2011) Recent advances in lipid nanoparticle formulations with solid matrix for oral drug delivery. AAPS PharmSciTech 12:62–76. https://doi.org/10.1208/S12249-010-9563-0
77 Hua X, Xu S, Wang M et al (2017) Effects of high-speed homogenization and high-pressure homogenization on structure of tomato residue fibers. Food Chem 232:443–449. https://doi.org/10.1016/J.FOODCHEM.2017.04.003
78 Puglia C, Bonina F (2012) Lipid nanoparticles as novel delivery systems for cosmetics and dermal pharmaceuticals. Expert Opin Drug Deliv 9:429–441. https://doi.org/10.1517/17425247.2012.666967
79 Anton N, Benoit JP, Saulnier P (2008) Design and production of nanoparticles formulated from nano-emulsion templates—a review. J Control Release 128:185–199. https://doi.org/10.1016/J.JCONREL.2008.02.007
80 Ren G, Sun Z, Wang Z et al (2019) Nanoemulsion formation by the phase inversion temperature method using polyoxypropylene surfactants. J Colloid Interface Sci 540:177–184. https://doi.org/10.1016/J.JCIS.2019.01.018
81 Jintapattanakit A (2018) Preparation of nanoemulsions by phase inversion temperature (PIT) method. Pharm Sci Asia 45:1–12. https://doi.org/10.29090/PSA.2018.01.001
82 Duong V-A, Nguyen T-T-L, Maeng H-J (2020) Preparation of solid lipid nanoparticles and nanostructured lipid carriers for drug delivery and the effects of preparation parameters of solvent injection method. Molecules 25:4781. https://doi.org/10.3390/MOLECULES25204781
83 Patil D, Pattewar S, Palival S et al (2019) Nanostructured lipid carriers: A platform to lipophilic drug for oral bioavailability enhancement. J Drug Deliv Ther 9:758–764. https://doi.org/10.22270/JDDT.V9I3-S.2750
84 Corrias F, Lai F (2011) New methods for lipid nanoparticles preparation. Recent Pat Drug Deliv Formul 5:201–213. https://doi.org/10.2174/187221111797200597
85 Friberg SE, Corkery RW, Blute IA (2011) Phase inversion temperature (PIT) emulsification process. J Chem Eng Data 56:4282–4290. https://doi.org/10.1021/JE101179S
86 Mahant S, Rao R, Nanda S (2018) Nanostructured lipid carriers: Revolutionizing skin care and topical therapeutics. Design of nanostructures for versatile therapeutic applications. William Andrew Publishing, pp 97–136
87 Shidhaye S, Vaidya R, Sutar S et al (2008) Solid lipid nanoparticles and nanostructured lipid carriers—innovative generations of solid lipid carriers. Curr Drug Deliv 5:324–331. https://doi.org/10.2174/156720108785915087
88 Harde H, Das M, Jain S (2011) Solid lipid nanoparticles: an oral bioavailability enhancer vehicle. Expert Opin Drug Deliv 8:1407–1424. https://doi.org/10.1517/17425247.2011.604311

89 Chakravarty P, Famili A, Nagapudi K, Al-Sayah MA (2019) Using Supercritical fluid technology as a green alternative during the preparation of drug delivery systems. Pharmaceutics 11:629. https://doi.org/10.3390/PHARMACEUTICS11120629

90 Meziani MJ, Pathak P, Sun Y-P (2009) Supercritical fluid technology for nanotechnology in drug delivery. In: de Villiers MM, Aramwit P, Kwon GS (eds) Nanotechnology in drug delivery. Biotechnology: pharmaceutical aspects. Springer, New York, pp 69–104

91 Carneiro SP, dos Santos ODH (2020) Nanostructured lipid carrier-based drug delivery systems for tuberculosis treatment. In: Kesharwani P (ed) Nanotechnology based approaches for tuberculosis treatment. Academic Press, pp 193–205

92 Chattopadhyay P, Shekunov BY, Yim D et al (2007) Production of solid lipid nanoparticle suspensions using supercritical fluid extraction of emulsions (SFEE) for pulmonary delivery using the AERx system. Adv Drug Deliv Rev 59:444–453. https://doi.org/10.1016/J.ADDR.2007.04.010

93 Akbari Z, Amanlou M, Karimi-Sabet J et al (2020) Application of supercritical fluid technology for preparation of drug loaded solid lipid nanoparticles. Int J Nanosci Nanotechnol 16:13–33

94 Maniruzzaman M, Boateng JS, Snowden MJ, Douroumis D (2012) A Review of hot-melt extrusion: process technology to pharmaceutical products. ISRN Pharm 2012:1–9. https://doi.org/10.5402/2012/436763

95 Adler C (2017) New lipid-based formulation approaches and characterization tools for hot-melt extrusion. University of Basel

96 Bhagurkar AM, Repka MA, Murthy SN (2017) A novel approach for the development of a nanostructured lipid carrier formulation by hot-melt extrusion technology. J Pharm Sci 106:1085–1091. https://doi.org/10.1016/j.xphs.2016.12.015

97 Crowley MM, Zhang F, Repka MA et al (2007) Pharmaceutical applications of hot-melt extrusion: part I. Drug Dev Ind Pharm 33:909–926. https://doi.org/10.1080/03639040701498759

98 Patil H, Tiwari RV, Repka MA (2016) Hot-melt extrusion: from theory to application in pharmaceutical formulation. AAPS PharmSciTech 17:20–42. https://doi.org/10.1208/s12249-015-0360-7

 *Author -1*	***Author Name – Ms.Mhetre Rani Mallinath*** *Author Affiliation* *Amepurva Forums Dr.Ashok Gujar College of Pharmacy,Boramani Solapur Maharashtra -413006*
 *Author -2*	***Author Name- Dr.Tegeli Varsha*** *Author Affiliation* *DSTS Mandals College of Pharmacy, Solapur , Maharashtra -413004*
 *Author -3*	***Author Name- Mr.Lavate Amol B.*** *Author Affiliation* *Amepurva Forums Dr.Ashok Gujar College of Pharmacy,Boramani Solapur Maharashtra -413006*
 *Author -4*	***Author Name- Mr.Jadhav Rahul Ishwara*** *Author Affiliation* *Amepurva Forums Dr.Ashok Gujar College of Pharmacy,Boramani Solapur Maharashtra -413006*
 *Author -5*	***Author Name- Dr.Tiwari B.D.*** *Amepurva Forums Dr.Ashok Gujar College of Pharmacy,Boramani Solapur Maharashtra -413006*