Journal of Developing Drugs
ISSN: 2329-6631
Sharma and Baldi, J Develop Drugs 2018, 7:2
Review Article
Open Access

Nanostructured Lipid Carriers: A Review

Amit Sharma[1,2] **and Ashish Baldi**[3*]

[1]*Department of Pharmacy Practice, ISF College of Pharmacy, Punjab, India*

[2]*Research Scholar, Uttarakhand Technical University, Post office, Chandanwadi, Prem Nagar Sudhowala, Dehradun, 248001, Uttarakhand, India*

[3]*Department of Pharmaceutical Science and Technology, Maharaja Ranjit Singh Punjab Technical University, Punjab, India*

[*]**Corresponding author:** Ashish Baldi, Department of Pharmaceutical Science and Technology, Maharaja Ranjit Singh Punjab Technical University, Punjab, India, Tel: 8968423848; E-mail: baldiashish@gmail.com

Rec date: July 30, 2018; **Acc date:** August 06, 2018; **Pub date:** August 15, 2018

Abstract

Lipid-containing drug delivery systems like NLC are well-established methods for preparing pharmaceuticals for all major kind of drug delivery systems of nanoscience. Lipid formulations require a variety of product-related requirements and problems associated with NLC, which is discussed thoroughly in this chapter. There are multiple DDS currently available which leads to enhance the solubility of the drugs in different medium as well as also increase the bioavailability of the drugs in different conditions and environments. NLC's are a novel type of DDS which are stable in different environment and which have capabilities to form concentrated dispersions. In this chapter, we discussed different process variables, steps involved in the manufacturing of NLC and responses with their outcome. NLC's can increase the drug distribution to the target organ, change the pharmacokinetic characteristics of drug carriers to enhance the therapeutic effect, and reduce adverse side effects.

Keywords: Nano lipids carrier; Solid lipid nanoparticles; Controlled release; Bioavailability enhancer; Colloidal drug carrier

Introduction

Lipid-based (Drug Delivery System) DDS is a known, established, commercially viable approach to manufacture pharmaceuticals for different dosage forms [1]. Lipid formulations like (Nano Lipid Carriers) NLC's need a variety of the products to be incorporated in formulations. Mainly the bioavailability and solubility of the insoluble drugs are two main criteria which can be enhances with the formulations like NLC's [2]. Many pharmaceutical companies have developed a well-established industrial processes for the manufacturing of large-scale batches of nanostructured lipid carriers, but 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 [3,4].

Lipid nanoparticles show remarkable properties which are required and very essential for their therapeutic action. The exceptional properties of nanoparticles (NP) like surface to mass ratio are additional colloidal particles and their capability to bind and to carrying compounds which makes a NP to more smart to use as medicinal product [5].

Lipid nanoformulations 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* [6,7].

A lipid matrix is available inside the newly made NLC's having a very special nanostructure which was developed by Muller [3,8]. This special type of NLC's nanostructure also helps to increase bioavailability, drug loading and solubility of the drug in different conditions and environments [9]. There are multiple techniques and methods by which means these 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 [10].

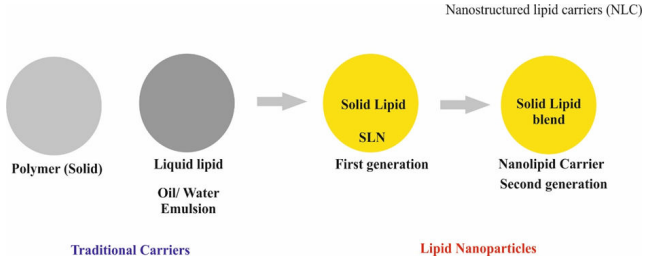

Figure 1: Nanostructured lipid carrier.

NLC's are a new type of DDS and formulation which provides better stability and loading with the capability to form concentrated dispersions [8,9,11]. Many pharmaceutical companies have developed some well-established industrial processes for the manufacturing of large-scale batches of nanostructured lipid carriers, but 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, size, phase transition, solubility, bioavailability of drug etc. if process variable like mixing and stirring (speed and time), melting (temperature), homogenization (speed,

temperature, pressure) are not followed as per standard guidelines an standard operating procedures.

NLC's are made up of a binary mixture of solid-lipid and a liquid-lipid (oil) as a hybrid carrier having an average size of 10-500 nm [12]. The mixture NLC's is consist of long chain of liquid and lipid (oil) of ratio 99.9: 0.1 and having a short chain of solid and lipid having a ratio of 70:30 [8] as shown in Figures 1 and 2 [12].

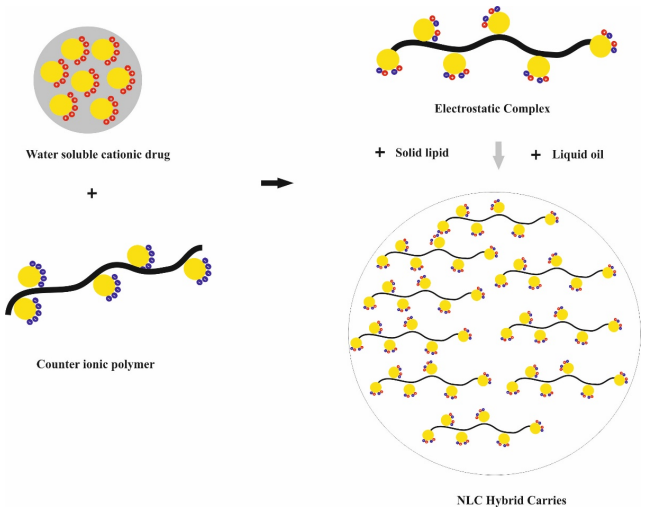

Figure 2: Mixture of solid- lipid with liquid-lipid for nano lipid carrier hybrid.

The first time NLC's was introduced in 1990s as another carrier system [13]. 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 [9]. 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 [14-17].

Structure of NLC's

The structure of NLS's are very and somehow similar to SLNs, NLCs have three very specific features [4]. These properties are based up on the location the drug is going to be integrated [14,16,17] 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 3 [18].

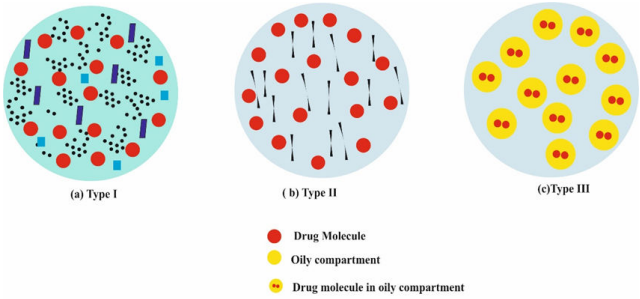

Figure 3: Drug molecule, oily compartment and drug molecule in oily compartment model of NLC's [18].

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 [4]. 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 [4].

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 [4].

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 [4,19,20]. 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 [8,14,21].

This kind of formulation permit controlled drug release and leakage of drug from lipid matrix [15]. 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 [4,22,23].

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 [4,24,25].

Drug release

The release of the drugs from a matrix is depends upon the rate of degradation and diffusion in case of NLC's. It is well documented in literature that it is compulsory to have exact and controlled release going beyond diffusion and degradation. The particle should be triggered by an impulse when a particle is administered the release [11].

The drug will have to trapped in NLC's because of their unordered and unorganized lipid structure. By applying different methods and techniques the structure of the lipid can be modified, which leads to convert the structure of lipid molecule and hence ongoing drug release can be initiated as shown in Figure 4. It was observed that this method is essential in case of NLC's are incorporated in cream for use in the skin as well as for the treatment of different dermatological problems like psoriasis, ezema. These type of NLC's are useful and have very advantageous properties if used by rubbing it increases the temperature and water evaporation from the formulation, based upon this method cyclosporine-lipid particles are under development to treat psoriasis [8,11,16,26-29].

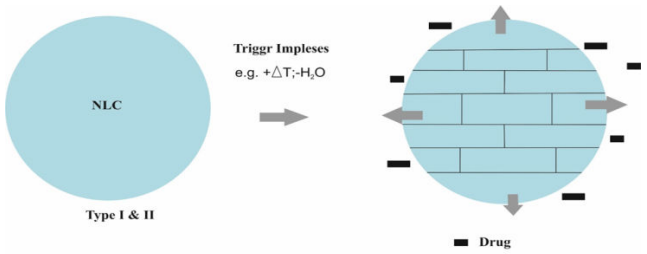

Figure 4: The drug release from NLC by initiating the alteration from a extremely disordered lipid structure to more ordered stable modifications [9].

It was observed that in case of SLNs particle aggregation can occur during long-term storage of dispersions [9,30]. The collision of the particle can cause perkinetic flocculation in the very concentrated NLC dispersions the particles form a pearl-like network, so particle required be in a fixed position to avoid a collision and perikinetic flocculation as shown in Figure 5 [30-34].

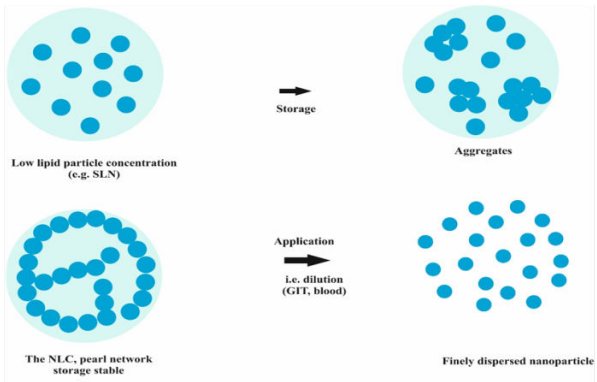

Figure 5: Aggregates formation from lipid particle after storage and pearl-like network in NLC's dispersions [9,12,30].

Advantages of NLC's

- NLC's are easier to validate and get easily approval from regularity bodies [11,35,36].
- NLC has excellent biocompatibility [37].
- Organic solvents can be avoided as it is water-based methods [38].
- NLC's are easy to scale-up and sterilize, inexpensive as compare to polymeric/surfactant-based carriers [39].
- NLC's provide the control and/or target drug release to improving the stability of pharmaceuticals [11].
- NLC's delivers great and higher drug content as related to other carriers available in the market [11].
- NLC's have possibilities of transport both lipophilic and hydrophilic drugs on same time [40].
- Most lipids being biodegradable [41].

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 behaviour of the formulations [4]. 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 [4]. Selection of appropriate lipids is essential prior to their use in preparation of lipid nanoparticle dispersions [4]. 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 [42,43] 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 [2,4,36]. 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) [44,45].

Solid lipids

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

These solid lipids are well tolerated [46-48].

- 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. [46-48] as shown in Table 1.

Fatty acids	Dodecanoic acid, Myristic acid, Palmitic acid and Stearic acid.
Monoglycerides	Glyceryl monostearate, and Glyceryl behenate.
Diglycerides	Glyceryl palmitostearate and Glyceryl dibehenate.
Triglycerides	Caprylate triglyceride, Caprate triglyceride, Glyceryl and tribehenate/Tribehenin.
Waxes	Cetyl Palmitate, Carnauba, and wax Beeswax.
Liquid lipids	Soya bean oil, Oleic acid, Medium chain triglycerides (MCT)/caprylic- and capric triglycerides, α-tocopherol/Vitamin E, Squalene Hydroxyoctacosanyl hydroxystearate and Isopropyl myristate.
Cationic lipids	Cetyl pyridinium chloride (hexadecyl pyridinium chloride, CPC), Cetrimide (tetradecyl trimethyl ammonium bromide, CTAB.

Table 1: Lipids used in the preparation of nanostructured lipid carriers [3,4].

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 [3,4,31]. At low concentrations, surfactants adsorb onto the surface of a system or interface [4,36]. Surfactant decreases the surface or interfacial free energy and decrease the surface or interfacial tension between the two phases [2,4,23].

The categories and type of surfactants are mentioned in Table 2 [4]. The selection of surfactants for NLCs based upon a number of multiple factors, like route of administration of NLCs, HLB value of surfactant [4,49]. The surfactants and co-surfactants are given in Table 2 [4,50-52].

Surfactants	
Ionic surfactants	**Non-ionic surfactants**
Sodium taurodeoxycholate, Sodium oleate, Sodium dodecyl sulphure [4,12,24].	Span 20, 80, 85, Tween 20, 80, Tyloxapol, Poloxamer 188 Poloxamer 407, Solutol HS15 [4,12,24].
Amphoteric surfactants	**Co-surfactants**
Egg phospholipid (Lipoid E 80, Lipoid E 80 S) Soy	Butanol, Butyric acid [4,15,17].
Hydrogenated soy phosphatidylcholine (Lipoid S PC-3,	
Hydrogenated egg phosphatidylcholine (Lipoid E PC-3)	
Phospholipon 80 H, Phospholipon 90 H)	

Table 2: Classification of surfactants and co-surfactants for the preparation of NLC's [4,44].

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 [4,8,17]. The addition of polysorbate 80 possibly provided more interfacial area than polysorbate 20 [4]. 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 [53]. The type of stabilizer significantly affected the average size and charge but not the size distribution of the NLCs [4,54].

NLCs have excellent features and properties that can rise the presentation of a variability of integrated drug forms [4]. The properties of the NLCs are really influenced by the type of surfactant used [4,37,55].

The Effect of surfactant concentration on the particle size and particle size distribution of NLC [4]. NLC can be stable by creating electrostatic and steric repulsion between particles. Some properties of both electrostatic and steric repulsion are mentioned [31,35]. 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 [37,48]. 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 [19,48]. 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 [56,57].

Surface modifiers

- Dipalmitoyl-phosphatidyl-ethanolamine conjugated with polyethylene glycol 2000 (DPPE-PEG2000).
- Distearoyl-phosphatidyl-ethanolamine-N-poly (ethylene glycol) 2000 (DSPE-PEG2000)
- Stearic acid-PEG 2000 (SA-PEG2000).
- α-methoxy-PEG 2000-carboxylic acid-α-lipoamino acids (mPEG2000-C-LAA18).
- α-methoxy-PEG 5000-carboxylic acid-α-lipoamino acids (mPEG5000-C-LAA18) [4,17,46,58,59].
- Ionic polymers: Dextran sulphate sodium salt.

Excipients for NLCs

The solid lipids commonly used for NLCs include glyceryl behenate (Compritol® 888 ATO), glyceryl palmitostearate (Precirol® ATO 5), fatty, steroids and waxes. These lipids are solid at room temperature. They melt at higher temperatures (e.g. > 80°C) during the preparation. Liquid oils typically used for NLCs consist of digestible oils obtained from natural sources [11,24-26]. The excipients used for the preparation of NLC's are shown in Table 3 [11,24-26].

Ingredient	Material
Solid lipids	Gelot® 64, Emulcire® 61, Tristearin, stearic acid, Softisan® 154, Cutina® CP, Imwitor® 900 P, Geleol®, cetyl palmitate [4,16,26].
Liquid lipids	Lauroglycol® FCC, Capryol® 90, Medium chain triglycerides, paraffin oil, 2-octyl dodecanol, Miglyol® 812, Transcutol® HP, Labrafil Lipofile® WL 1349, Labrafac® PG [4,21,26].
Hydrophilic emulsifiers	Polyvinyl alcohol, Solutol® HS15, polyglycerol methyl glucose distearate Pluronic® F68 (poloxamer 188), Pluronic® F127, Tween 20, Tween 40, Tween 80 [4,26,60].
Lipophilic emulsifiers	Span 40, Span 60, Myverol® 18-04K, Span 20 [4,26,61].
Amphiphilic emulsifiers	Egg lecithin, soya lecithin, phosphatidylcholines, phosphatidylethanolamines, Gelucire® 50/13 [4,26].

Table 3: Excipients used for the preparation of NLC's.

Methods of preparation of NLS's

There are several methods are developed for the preparation of NLS's [62]. The most command methods are as follows:

- High-pressure homogenization.
- Microemulsion technique.
- Emulsification-solvent diffusion.
- Emulsification-solvent.
- Evaporation solvent injection.
- Multiple emulsion techniques.
- Phase inversion.
- Ultrasonication.
- Membrane contractor technique [62].

Methods of preparation lipid screening

The screening of lipids stepwise, for the preparation of NLC's are shown stepwise in Figure 6 [24]

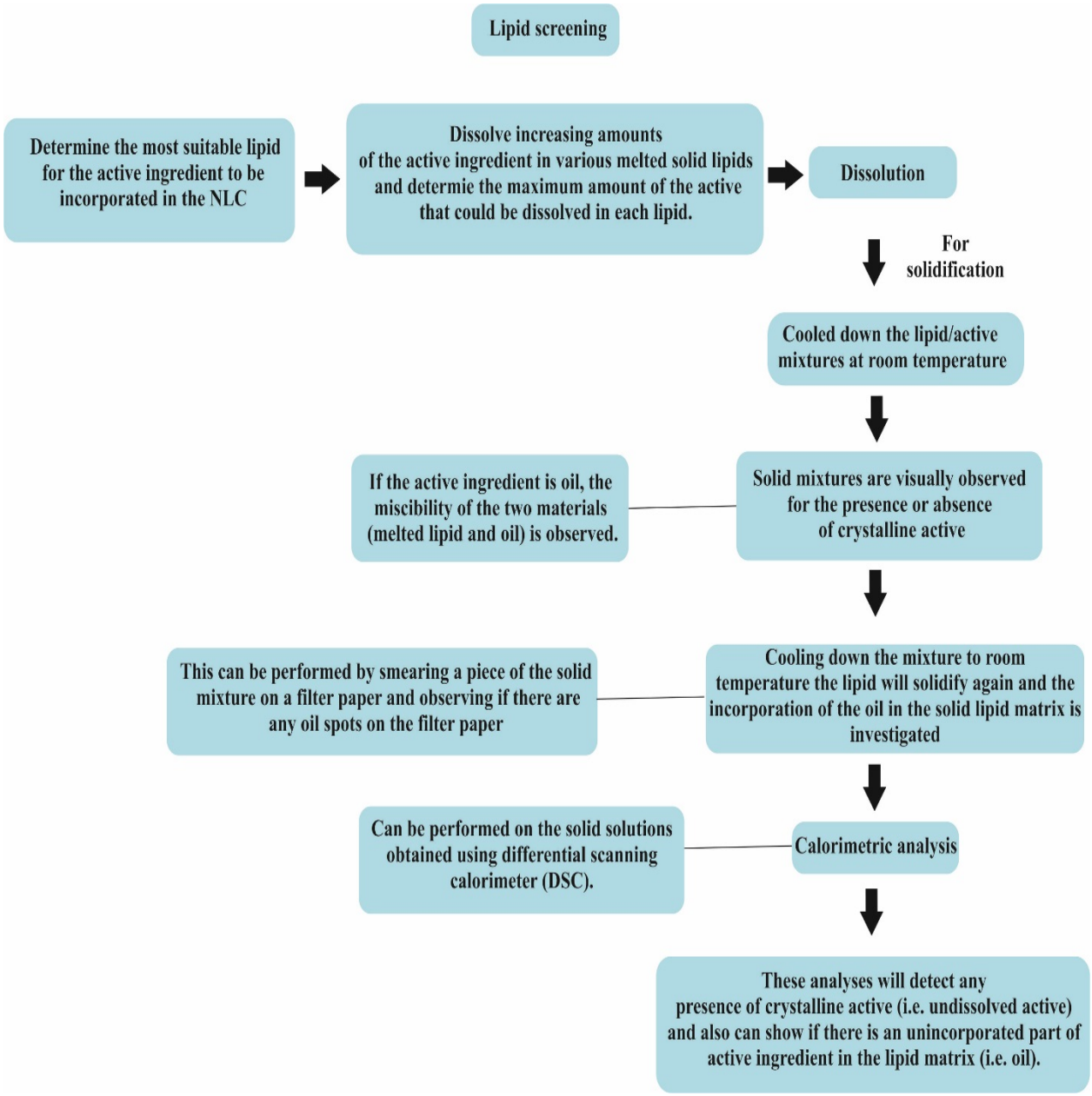

Figure 6: Lipid screening for preparation of NLC.

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 7 [8,11,60].

- Hot homogenization [11].
- Cold homogenization [24].
- 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 [8,11,20,46].

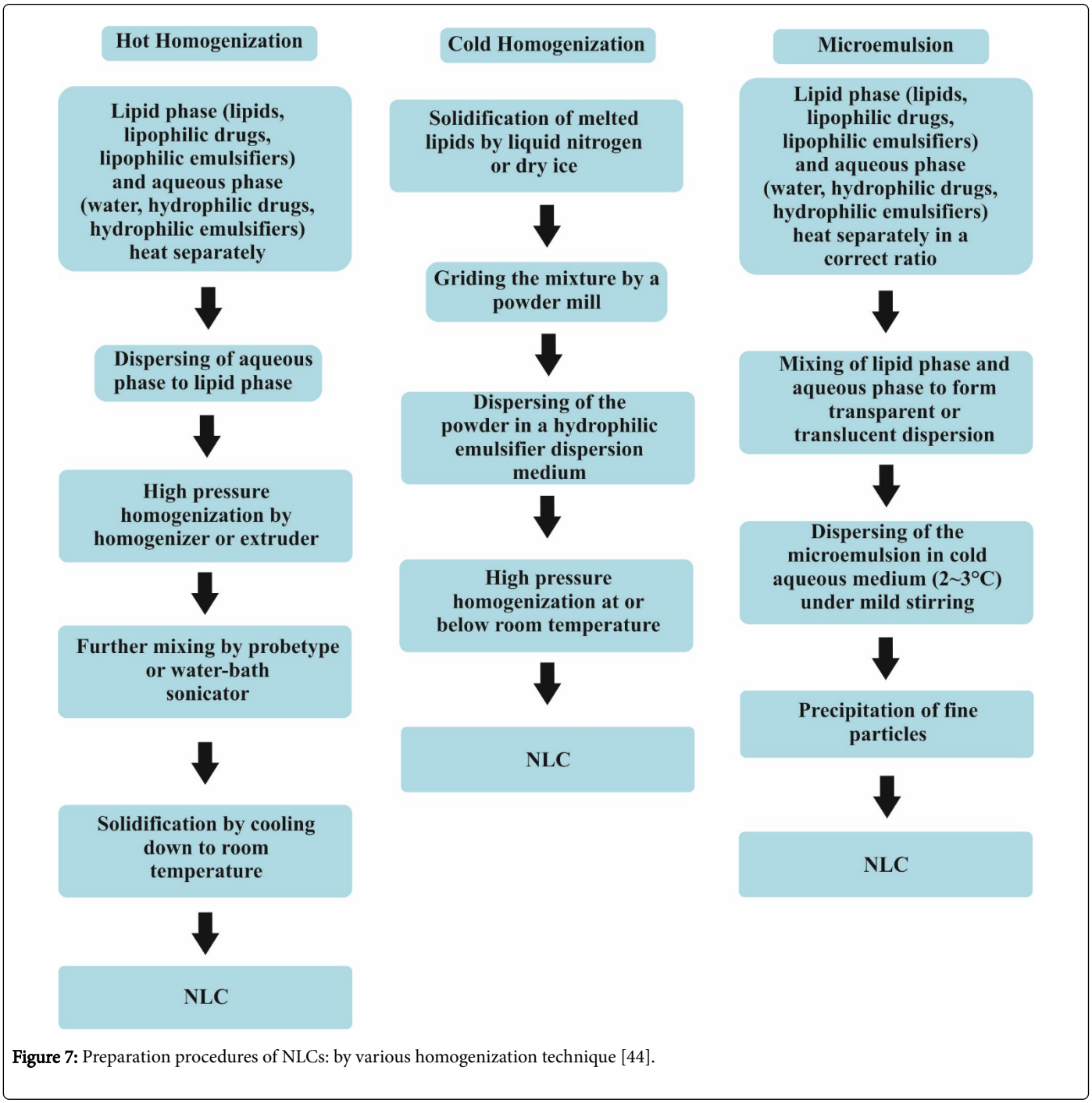

Figure 7: Preparation procedures of NLCs: by various homogenization technique [44].

Advantages

- Wisely used in the food and dairy industries and cosmetic industry.
- It improves product shelf life, stability, digestion.
- It improves the taste of the formulation.
- It significantly reduces the number of additives.
- Essential for quality and stability of the products in the cosmetic industry.
- By homogenization bioavailability of the formulation can be enhanced.
- Economical.
- Microbiological contamination is clearly less.

The bioavailability may be enhanced by increasing the solubility and dissolution rate of the drug in the gastrointestinal fluids. The main possibilities for improving dissolution according to this analysis are to increase the surface area available for dissolution by decreasing the particle size of the solid compound and/or by optimizing the wetting characteristics of the compound surface, to decrease the boundary layer thickness to ensure sink conditions for dissolution, and, last but definitely not least, to improve the apparent solubility of the drug under physiologically relevant conditions [11].

Melt dispersion ultrasonication method

The detailed procedure of melt dispersion and aqueous dispersion ultrasonication method is shown in Figures 8 and 9.

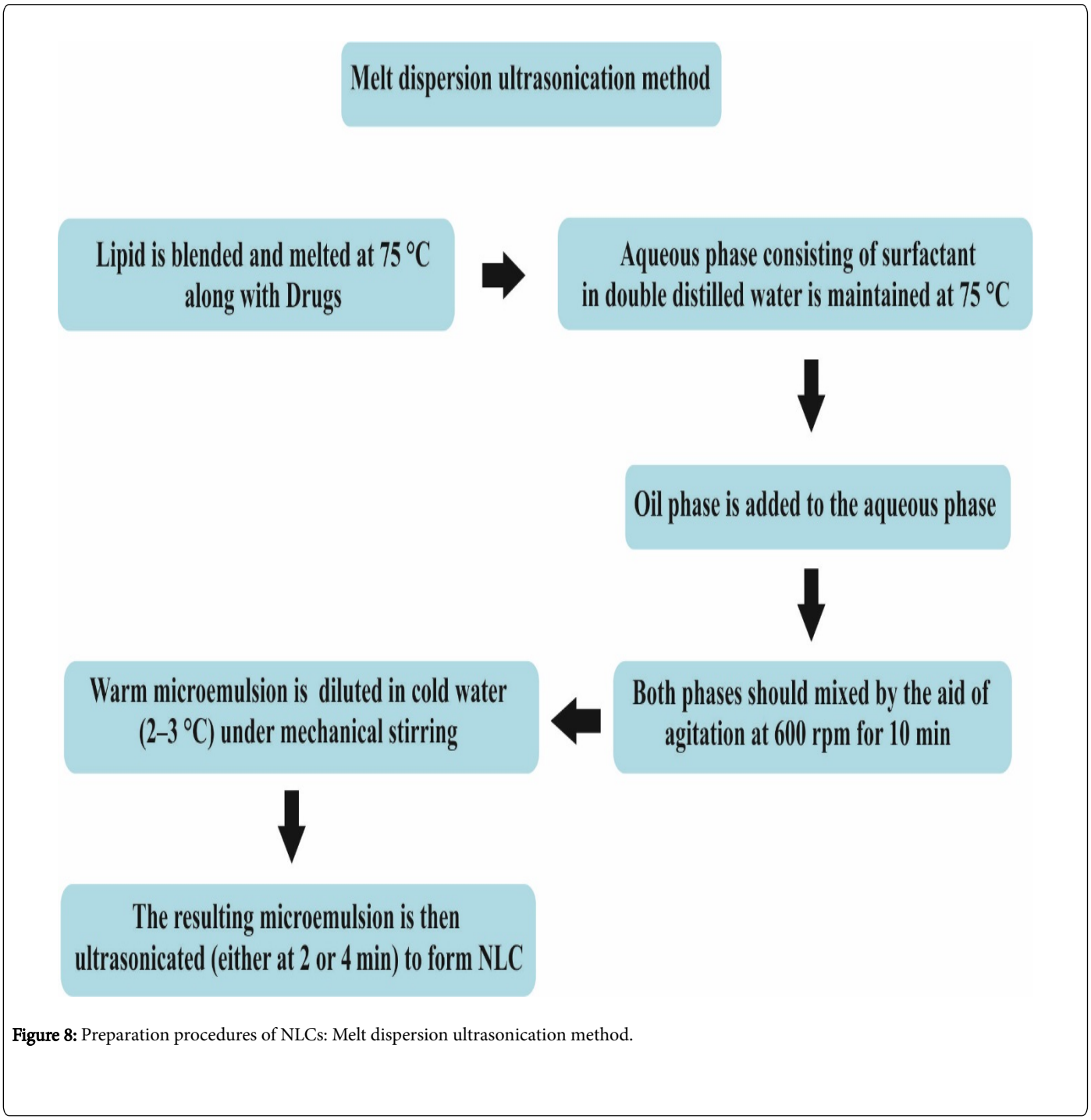

Figure 8: Preparation procedures of NLCs: Melt dispersion ultrasonication method.

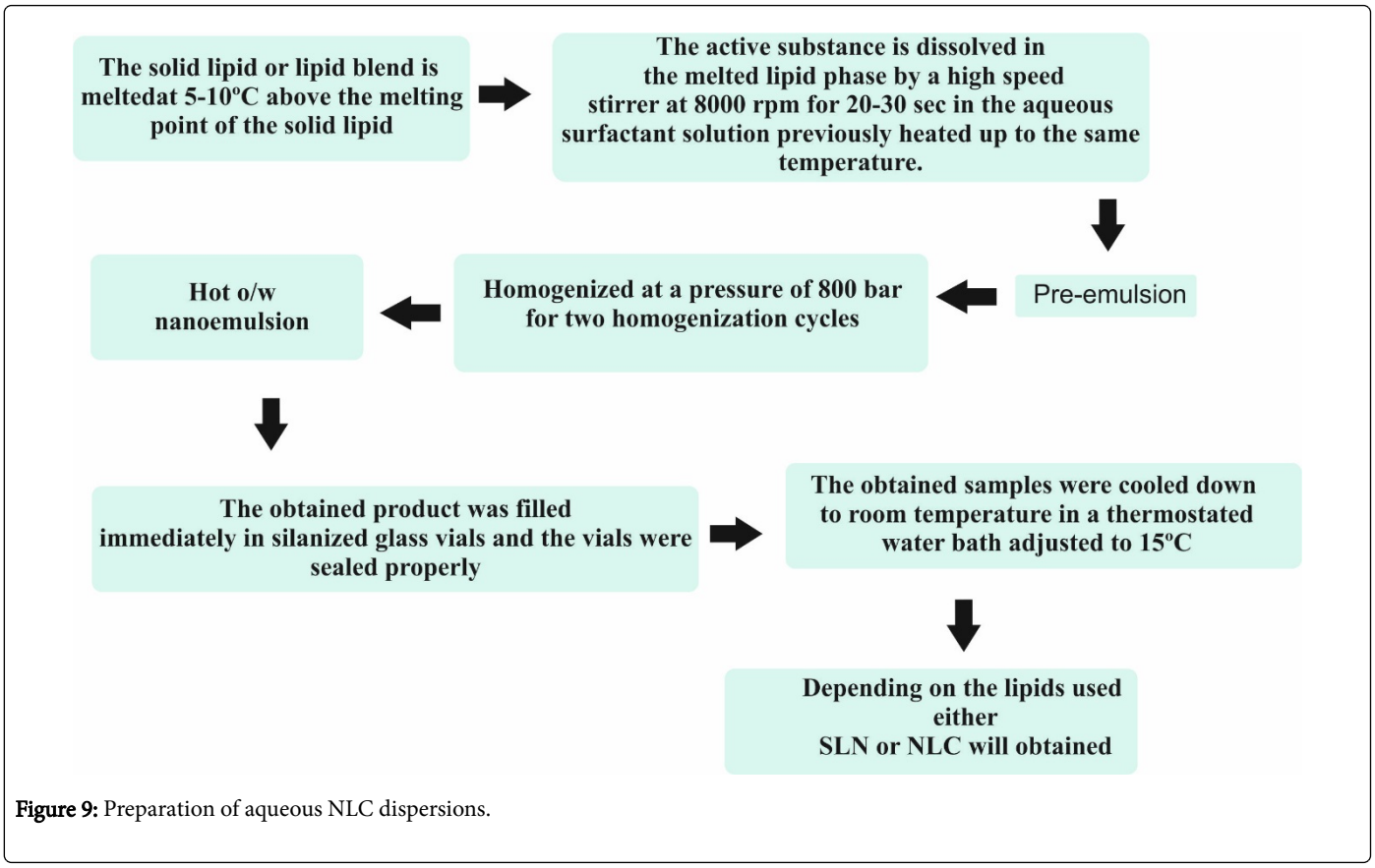

Figure 9: Preparation of aqueous NLC dispersions.

The quality and effectiveness of lipid nanoparticles are influenced by the surfactant properties and mainly by their concentration, particle size, parameters of the preparation process, crystallinity, dispersion stability [60-64].

The critical material attributes and critical process characteristics, process variables of NLC are discussed in detail and shown in Tables 4 and 5 [63].

Excipients Attribute	
Excipient	**Specification**
Selection of solid lipid	Based on high solubility lipid were selected for preparation of NLC. This is done by dissolving increasing quantities of the ingredient in melted solid lipids and determining the highest amount of the action that could be dissolved in each lipid. Drug solubility should be evaluated in Compritol 888 to and Precirol ATO, stearic acid, glyceryl monostearate [36,63].
Selection of liquid lipid	For the selection of liquid lipid, the trial batches should be prepared with fixed ratio of liquid lipid to solid lipid (GMS). The example of liquid lipid such as (oleic acid, caprylic/capric triglyceride and propylene glycol dicaprylate/caprate) [36,63].
Selection of surfactants	The structure of the lipid nanoparticles is affected during formulation so surfactant is used to stabilize the particles in the dispersion media. Based on the HLB and molecular weight surfactant and the of the surfactant molecules, the affinity of the surfactant to the lipid differs. Based upon the HLB value of the surfactant and the molecular weight of the surfactant molecules suitable surfactants should be chosen [2,11,63,65].
Process Parameter	
Parameter	**Specifications**
Melting	Melting should be done at 85°C to ensure a complete melting and 5-10ºC above the melting point of the solid lipid [11,63]
Mixing by Stirring	Stirring should be done at 85°C and stirrer should be at 8000 rpm for 20-30 second to confirm mixing of active ingredients with lipids [11,63].
cooling	Should be performed at room temperature for solidification [11,63] The samples were cooled down at room temperature in a thermostatic water bath at 15ºC [10,11].

Solidification test (oil in the solid lipid matrix) Smearing	This can be done by smearing a piece of the solid mixture on a filter paper and observing if there are any oil spots on the filter paper [11,27,36,52,63].
Calorimetric analysis	Can be done on the solid solutions obtained using differential scanning calorimeter. These analyses will detect any presence of crystalline active and also can show if there is an unincorporated part of an active ingredient in the lipid matrix (i.e., oil) [11,63,66].
Temperature	The lipid (oil) phase and the aqueous surfactant solution were heated up to about 80ºC. Temperature also affects the zeta potential. NLC can be stored in temperature between 5°C to 25°C. Depending on the temperature, in which NLC stored particle size differs [8,11,63].
Particle size	Very important for the stability of the NLC. Techniques were direct measurements (microscopy) and indirect measurements (laser diffractometry and photon correlation spectroscopy) [8,11,63].
Homogenization Speed: 8000-16000 rpm	The homogenization speed ranges were selected based on instrument limitation and trial batches. The homogenization speed less than 8000 rpm leads to large particle size and polydisperse colloidal system. However, the upper range should be selected e.g., 16000 rpm. Homogenization pressure of 800 bar and two homogenization cycles [8,11,63].
Pressure: 800 bar	
Homogenization Temperature	Homogenization should be performed at higher temperatures (80-90ºC) [11,49,63].
Sonication time: 5-15 min	The time duration for sonication was selected based on the literature and trial batches. Moreover, longer duration of sonication was avoided due to leaching of the drug from the matrix and possible metal contamination [11,31,63,67].
Physical stability	Physical stability can be evaluated by measuring the zeta potential.
	• Zeta potential- 30 mV - colloidal system is in stable state
	• Zeta potential- 60 mV - super high stability
	• Zeta potential- 15 mV - severe aggregation [8,11,16,63].
Polydispersity index (PI)	Is the measure of the equal distribution of nanoparticle population? PI is carried out by dynamic light scattering (DLS) using Malvern Zetasizer 2000MU (Malvern, UK, detection limit 0.01–1,000 μm) [11,14,63].

Table 4: Excipient and their specifications for nanostructured lipid carriers (NLCs)[25].

Process Variables	Step involved	Process Responses
Speed and Time	Mixing	Particle shape, Particle size
Temperature	Melting	Phase transition, Solubility
Speed and Time	Stirring	Particle shape, Particle size
Speed, Temperature, Pressure	Homogenization	Particle size, Particle shape

Table 5: Process variables and their role in the preparation of NLCs.

Conclusion

The NLC's are the carrier systems with suitable perspectives to be marketed very successfully. The NLC's are the new generation of formulations which offer much more flexibility in drug loading, modulation of release and improved performance in producing final dosage forms such as injectable, creams, tablets, capsules etc. Because of the great consistency of NLC dispersions, they can be used as numerous formulations. This special type of NLC's nanostructure also helps to increase bioavailability, drug loading and solubility of the drug in different conditions and environments and these carriers can increase the drug distribution to the target organ, change the pharmacokinetic characteristics of drug carriers to enhance the therapeutic effect, and reduce adverse side effects.

References

1. 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.
2. Xia Q, Wang H (2010) Preparation and characterization of coenzymes Q-10 loaded NLC. NSTI-Nanotech 3: 498-501.
3. 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.
4. Shah R, Eldridge D, Palombo E, Harding I (2015) Lipid Nanoparticles: Production, Characterization and Stability. Briefs Pharm Sci Drug Dev 1: 11-23.
5. Riessman C (2010) University of Huddersfield Repository. Narrative, memory and everyday life.
6. Jaiswal P, Gidwani B, Vyas A (2016) Nanostructured lipid carriers and their current application in targeted drug delivery. Artif Cells Nanomed Biotechnol 44: 1-14.
7. 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.
8. Radtke M, Müller RH (1991) Nanostructured Lipid Carriers: A novel generation of solid lipid drug drug Carriers. Pharmaceutical Technology Europe 17: 1-4.
9. Peddinti S (2016) Nanostructured lipid carriers as a drug carrier. J Pharm Nanotechnol Nanostruc 4: 68-74.
10. Dubey A, Prabhu P, Kamath JV (2012) Nano structured lipid carriers: A novel topical drug delivery system. Int J PharmTech Res 4: 705-714.
11. Purohit DK, Nandgude TD, Poddar SS (2016) Nano-lipid carriers for topical application: Current scenario. Asian J Pharm 10: 1-9.

12. Charcosset C, El-Harati A, Fessi H (2005) Preparation of solid lipid nanoparticles using a membrane contactor. J Control Release 108: 112-120.
13. 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.
14. 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.
15. 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.
16. Jenning V, Gohla S (2000) Comparison of wax and glyceride solid lipid nanoparticles. Int J Pharm Sci 196: 219-222
17. 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.
18. Lopes CPA (2014) Development and Characterization of Lipid Nanoparticles prepared by Miniemulsion Technique.
19. Radtke M, Muller R (2001) Nanostructured lipid drug carriers. New Drugs 48-52.
20. 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.
21. Arunkumar N, Deecaraman M, Rani C (2014) Nanosuspension technology and its applications in drug delivery. Asian J Pharm 3: 168.
22. Persson LC, Porter CJH, Charman WN, Bergström CAS (2013) Computational prediction of drug solubility in lipid based formulation excipients. Pharm Res 30: 3225-3237.
23. Karunakar G, Patel NP, Kamal SS (2016) Nano structured lipid carrier based drug delivery system. J Chem Pharm Res 8: 627-643.
24. 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.
25. Kaur S, Nautyal U, Singh R, Singh S, Devi A (2015) Nanostructure Lipid Carrier (NLC): the new generation of lipid nanoparticles. Asian Pacific J Heal Med 2: 76-93.
26. Uner M (2006) Preparation, characterization and physico-chemical properties of solid lipid nanoparticles (SLN) and nanostructured lipid carriers (NLC): their benefits as colloidal drug carrier systems. Pharmazie 61: 375-386.
27. Zirak MB, Pezeshki A (2015) Effect of surfactant concentration on the particle size, stability and potential zeta of beta carotene nano lipid carrier. Int J Curr Microbiol Appl Sci 4: 924-932.
28. McEvoy SD, Sittig Dean F, Thu HT, Aaron S, Angela AI, et al. (2016) Variation in high-priority drug-drug interaction alerts across institutions and electronic health records. J Am Med Informatics Assoc 24: 331-338.
29. Anuradha K, Kumar S (2014) Development of Lacidipine loaded nanostructured lipid carriers (NLCs) for bioavailability enhancement. Int J Pharm Med Res 2: 50-57.
30. 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.
31. Chen M, Stitt A (2016) Animal Models of Diabetic Retinopathy. Curr Diab Rep 17: 67-83.
32. López-García R, Ganem-Rondero A (2015) Solid lipid nanoparticles (SLN) and nanostructured lipid carriers (NLC): occlusive effect and penetration enhancement ability. J Cosmet 5: 62-72.
33. Carrier L (2006) Formulation and Evaluation of Nanostructured Lipid Carrier 8: 304-309.
34. Patwekar SL, Pedewad SR, Potulwar AP, Gaikwad MS (2016) Nanostructured lipid carriers in stability improvement for cosmetic nanoparticles. Int J Pharm Pharm Res 6: 168-180.
35. 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.
36. Board BMA (2006) Reporting adverse drug reactions a guide for healthcare professionals. BMA Board Sci 6: 147-158.
37. Fretheim A, Odgaard-Jensen J, Brørs O, Madsen S, Njølstad I, et al. (2012) Comparative effectiveness of antihypertensive medication for primary prevention of cardiovascular disease: systematic review and multiple treatments meta-analysis. BMC Med 10: 33.
38. Pallerla SM, Prabhakar B (2013) A review on solid lipid nanoparticles. Int J Pharm Sci Rev Res 20: 196-206.
39. Singh P, Gupta RK, Jan R, Raina SK (2017) Original Article Adherence for medication among self-reporting rural elderly with diabetes and hypertension. J Med Soc 31: 86-89.
40. Ravichandar R, Jamuna RR, Varadarajan S (2016) Article Study of adverse drug reactions in a tertiary care teaching hospital. IJBCP 5: 209-212.
41. Nguyen HM, Hwang IC, Park JW, Park HJ (2012) Enhanced payload and photo-protection for pesticides using nanostructured lipid carriers with corn oil as liquid lipid. J Micro Encapsul 29: 596-604.
42. Das RJ, Baishya K, Pathak K (2013) Recent advancement of lipid drug conjugate as nanoparticulate drug delivery system. Int Res J Pharm 4: 128-131.
43. 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.
44. Fang CL, Al-Suwayeh SA, Fang JY (2012) Nanostructured Lipid Carriers (NLCs) for Drug Delivery and Targeting. Recent Pat Nanotechnol 7: 41-55.
45. Upreti T (2017) Nanostructured Lipid Carrier System for the Treatment for Skin Disease-A Review. JSM Nanotechnol Nanomedicine 5: 1059.
46. Chen PC, Huang JW, Pang J (2013) An investigation of optimum NLC-sunscreen formulation using taguchi analysis. J Nanomater pp: 1-11.
47. Joshi M, Patravale V (2006) Formulation and Evaluation of Nanostructured Lipid Carrier (NLC)–based Gel of Valdecoxib. Drug Dev Ind Pharm 32: 911-918.
48. 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.
49. Ekambaram P, Sathalia AH, Priyanka K (2012) Solid Lipid Nanoparticles: A Review. Sci Rev Chem Commun 2: 80-102.
50. Doktorovova S (2009) Lipid nanoparticle mediated drug delivery for safer cancer treatment: example of paclitaxel. Rev da Fac Ciências da Saúde 6: 84-93.
51. Patron C, Convener W (2017) Workshop on research methodology and data analysis through SPSS.
52. Gupta S, Nayak R, Rahavi R, Kumar A (2015) A cross-sectional retrospective study to assess the pattern of prescribing for inpatient hypertensive cases in a tertiary hospital and to find out the possible avenues for betterment of hypertension management. Arch Med Heal Sci 3: 60.
53. 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.
54. Spitzer RL, Williams JBW, Kroenke K (2001) Patient Health Questionnaire (PHQ-9). J Gen Intern Med 16: 606-613.
55. Cheng J, Xu S, Wen L, Chen J (2005) Steric repulsion between internal aqueous droplets and the external aqueous phase in double emulsions. Langmuir 21: 12047-12052.
56. Chinsriwongkul A, Chareanputtakhun P, Ngawhirunpat T, Rojanarata T, Sila-on W, et al. (2012) Nanostructured lipid carriers (NLC) for parenteral delivery of an anticancer drug. AAPS PharmSciTech 13: 150-158.

57. Singhal GB, Patel RP, Prajapati BG, Patel NA (2011) Solid Lipid Nanoparticles and Nano Lipid Carriers: As novel solid lipid based drug carriers. Int Res J Pharm 2: 40-52.
58. Kamble SS, Gambhire MS, Gujar KN (2015) Optimization and development of candesartan cilexetil loaded solid lipid nanoparticle for the treatment of hypertension. J Pharm Biosci 3: 53-64.
59. Jain NK, Ram A (2011) Development and characterization of nanostructured lipid carriers of oral hypoglycemic agent: selection of surfactants. Int J Pharm Sci Revier Res 7: 125-130.
60. Kadam VB, Dhanawade KB, Salunkhe VA, Ubale AT (2014) Nanoparticle - novel drug delivery system. J Curr Pharma Res 4: 1318-1335.
61. ICH (2009) In: ICH Harmonised Tripartite Guideline. Pharmaceutical Development 8 pp: 1-28.
62. Sanap GS, Mohanta GP (2013) Design and evaluation of miconazole nitrate loaded nanostructured lipid carriers (NLC) for improving the antifungal therapy. J Appl Pharm Sci 3: 46-54.
63. Ashjaran A, Namayi A (2014) Survey on nanofiber material as drug delivery systems. Res J Pharm Biol Chem 5: 1262-1274.
64. Patidar A, Thakur DS, Kumar P, Verma J (2010) A review on novel lipid based nanocarriers. Int J Pharm Pharm Sci 2: 30-35.
65. Naseri N, Valizadeh H, Zakeri-Milani P (2015) Solid lipid nanoparticles and nanostructured lipid carriers: Structure preparation and application. Adv Pharm Bull 5: 305-313.
66. Joshi M, Patravale M (2006) Formulation and evaluation of nanostructured lipid carrier (NLC)-based gel of Valdecoxib. Drug Dev Ind Pharm 32: 911-918.
67. Hans ML, Lowman AM (2002) Biodegradable nanoparticles for drug delivery and targeting. Current Opinion in Solid State and Materials Science 6: 319-327.