Nanostructured Lipid Carriers: A Review

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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) NLCs 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 enhanced with the formulations like NLCs [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 NLCs 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 NLCs. 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 NLCs

The structure of NLSs 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].

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 NLCs 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 NLCs, the solubility of oil is greater as compare to solubility of solid lipids. In type II NLCs 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 NLSs also called as amorphous type. In this technique of preperation 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].

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/Tripehenin.

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>
<thead>
<tr>
<th>Table 1: Lipids used in the preparation of nanostructured lipid carriers [3,4].</th>
</tr>
</thead>
</table>

### 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 [2,4,37].

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

The combination of solid and liquid- lipid mixtures will not help much for 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
- α-methoxy-PEG 2000-carboxylic acid-α-lipoamino acids (mPEG2000-C-LAA18).
- α-methoxy-PEG 5000-carboxylic acid-α-lipoamino acids (mPEG5000-C-LAA18).
- 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. > 80ºC) 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 NLCs are shown in Table 3 [11,24-26].

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

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

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].
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 as follows and shown in Figure 7 [8,11,60].

- 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 6: Lipid screening for preparation of NLC.
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.
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].

**Figure 9:** Preparation of aqueous NLC dispersions.

<table>
<thead>
<tr>
<th>Excipients Attribute</th>
<th>Specification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Excipient Selection of solid lipid</td>
<td>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 [38,63].</td>
</tr>
<tr>
<td>Selection of liquid lipid</td>
<td>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].</td>
</tr>
<tr>
<td>Selection of surfactants</td>
<td>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].</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Process Parameter</th>
<th>Specifications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Melting</td>
<td>Melting should be done at 85°C to ensure a complete melting and 5-10°C above the melting point of the solid lipid [11,63]</td>
</tr>
<tr>
<td>Mixing by Stirring</td>
<td>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].</td>
</tr>
<tr>
<td>Cooling</td>
<td>Should be performed at room temperature for solidification [11,63] The samples were cooled down at room temperature in a thermostatic water bath at 15°C [10,11].</td>
</tr>
</tbody>
</table>
Table 5: Process variables and their role in the preparation of NLCs.

<table>
<thead>
<tr>
<th>Process Variables</th>
<th>Step involved</th>
<th>Process Responses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Speed and Time</td>
<td>Mixing</td>
<td>Particle shape, Particle size</td>
</tr>
<tr>
<td>Temperature</td>
<td>Melting</td>
<td>Phase transition, Solubility</td>
</tr>
<tr>
<td>Speed and Time</td>
<td>Stirring</td>
<td>Particle shape, Particle size</td>
</tr>
<tr>
<td>Speed, Temperature, Pressure</td>
<td>Homogenization</td>
<td>Particle size, Particle shape</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Physical stability</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zeta potential- 30 mV</td>
<td>colloidal system is in stable state</td>
</tr>
<tr>
<td>Zeta potential- 60 mV</td>
<td>super high stability</td>
</tr>
<tr>
<td>Zeta potential- 15 mV</td>
<td>severe aggregation</td>
</tr>
</tbody>
</table>

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

Conclusion

The NLCs are the carrier systems with suitable perspectives to be marketed very successfully. The NLCs 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


51. Pateron C, Conuver W (2017) Workshop on research methodology and data analysis through SPSS.


