Different Methodology for Preparation of NLCs - A Review

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ABSTRACT

Nanotechnology in the formulation developed exponentially, the main objective or the basic aim has been on therapeutic undertaking, particularly for targeted drug therapy. Nanocarriers are at forefront of the rapidly developing field of nanotechnology with several potential applications in novel drug delivery, also in clinical medicines and research. Solid lipid nanoparticles are at the forefront of the rapidly developing field of nanotechnology with several potential applications in medicinal formulation and other varied sciences. Due to their unique size-dependent properties, lipid nanoparticles offer the possibility to develop new therapeutic effect. The incorporation of drugs into nanocarriers offers a new prototype in drug delivery that could be used for different levels of drug targeting. Nanostructure lipid carriers have attracted expanding scientific and commercial vigilance in the last couple of years as alternate carriers for the pharmaceutical consignment. Today’s new generation of nanostructured lipid carriers (NLCs) consisting of a lipid matrix with a special nanostructured has been developed. This nanostructure improves drug loading and firmly incorporates the drug during storage. The present review gives insights on the definitions and different techniques of preparation of NLCs.

Keywords: Nanotechnology, Solid lipid nanoparticles, Nanocarriers, nanostructured lipid carriers, novel drug delivery
1. INTRODUCTION

Lipid-based drug delivery systems are promising drug carriers due to their ability to improve solubility of poorly water-soluble and/or lipophilic drugs which eventually enhance the oral bioavailability. The first generation of lipidic nanoparticles, the so-called solid lipid nanoparticles (SLNs), is composed of an aqueous dispersion of nanoparticles with a solid lipid matrix that is stabilized by one or more of surfactant layer. However, SLNs presented some drawbacks, such as limited drug loading capacity and potential tendency for drug expulsion during storage. Therefore, there is necessity to create second generation of lipidic nanoparticles, the nanostructured lipid carriers (NLCs). In contrast to SLNs, dispersions of NLCs are formed of a blend of solid lipid with liquid lipid, which provide a higher payload and prevent drug expulsion during storage. Higher drug loading is attributed to the differences in the chemical structure between liquid and solid lipids, which result in distortion of a perfect crystal and accommodation of drug in molecular form or in amorphous clusters. Moreover, NLC formulations have the advantages of prolonged drug release, biocompatibility and easy of scaling-up its production.\(^1, 2\)

Lipid nanoparticles made with a solid matrix (solid lipid nanoparticles, SLNs) are derived from oil-in-water nanoemulsions formed by replacing liquid oil with a solid lipid The first generation of SLNs was developed at the beginning of 1990 [3]. The advantages of SLNs are the use of physiological lipids, the avoidance of organic solvents, and the applicability of large-scale production. As drug delivery carriers, SLNs can improve bioavailability, protect sensitive drugs from a rigorous environment, and control drug-release characteristics [4]. Nevertheless, SLNs show some disadvantages as drug carriers including an unpredictable gelation tendency, polymorphic transition, and low incorporation due to the crystalline structure of solid lipids. At the turn of the millennium, nanostructured lipid carriers (NLCs) were developed to resolve, in some cases, the problems raised by SLNs. NLCs are produced by controlling the mixing of solid lipids with liquid oil, leading to special nanostructures in the matrix. The potential drawbacks of SLNs, such as limited drug-loading capacity and drug expulsion during storage, can be avoided by the new generation [5]. In this review we would like to show the current advance of NLCs for drug delivery and the targeting application. The various types of preparation techniques of NLCs discussed in the present review.

**Fig. Structure of NLCs**

The excipients for composing nanostructured lipid carriers (NLCs).\(^6, 7, 8, 9\)

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<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>Ingredients</th>
<th>Materials</th>
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<tbody>
<tr>
<td>1</td>
<td>Solid lipids</td>
<td>Tristearin, stearic acid, cetyl palmitate, cholesterol, Precirol® ATO 5, Compritol® 888 ATO, Dynasan® 116, Dynasan® 118, Softisan® 154, Cutina® CP, Imwitor® 900 P, Geleol®, Gelot® 64, Emulcire® 61</td>
</tr>
<tr>
<td>2</td>
<td>Liquid lipids</td>
<td>Medium chain triglycerides, paraffin oil, 2-octyl dodecanol, oleic acid, squalene, isopropyl myristate, vitamin E, Miglyol® 812, Transcutol® HP, Labrafil Lipophile® WL 1349, Labrafac® PG, Lauroglycol® FCC, Capryol® 90</td>
</tr>
<tr>
<td>3</td>
<td>Hydrophilic emulsifiers</td>
<td>Pluronic® F68 (poloxamer 188), Pluronic® F127 (poloxamer 407), Tween 20, Tween 40, Tween 80, polyvinyl alcohol, Solutol® HS15, trehalose, sodium deoxycholate, sodium glycocholate, sodium oleate, polyglycerol methyl glucose distearate</td>
</tr>
<tr>
<td>4</td>
<td>Lipophilic emulsifiers</td>
<td>Myverol® 18-04K, Span 20, Span 40, Span 60</td>
</tr>
<tr>
<td>5</td>
<td>Amphiphilic emulsifiers</td>
<td>Egg lecithin, soya lecithin, phosphatidylcholines, phosphatidylethanolamines, Gelucire® 50/13</td>
</tr>
</tbody>
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DIFFERENT TECHNIQUES FOR PREPARATION OF NANOSUSPENSION

1. High pressure homogenization (HPH)
2. Hot homogenization
3. Cold homogenization
4. Ultrasonication or high speed homogenization
5. Microemulsion
6. Phase inversion
7. Solvent Evaporation Technique
8. Double emulsion technique
9. Solvent emulsification-diffusion method
10. Spontaneous Emulsification
11. Microfluidization
12. Hydrogel Method

**1. High pressure homogenization (HPH) (10–16)**

High pressure homogenization technique used for the formulation of NLCs. High pressure homogenizers push a liquid with high pressure (100–2000 bar) through a narrow gap. The fluid accelerates on a small distance to high velocity (over 1000 Km/h). Very high shear stress and cavitation forces disrupt the particles down to the submicron range. Generally 5-10% lipid content is used but up to 40% lipid content has also been investigated.

High pressure homogenization is of two types: hot homogenization and cold homogenization. In this two, a formulation step gives the drug incorporation into the bulk lipid by dissolving or dispersing the drug in the lipid melt or liquid lipid.

**1. Hot homogenization (17-21)**

In this method, homogenization occurs at temperatures upper than melting point of lipid. Drug loaded lipid melt is dispersed in hot aqueous surfactants phase (isothermal) by mixing device (Ultra-Turrax) and leads to the formation of pre-emulsions. Because of the reduced viscosity at high temperatures, particle
size becomes lesser mainly. This technique is illustrated in Figure 2. Hot homogenization has three basic problems. The first is temperature-dependent degradation of the drug, the second is the drug penetrates into the aqueous phase during homogenization and the third is complexity of the crystallization step of the nano-emulsion leading to several modifications and/or super cooled melts.

2. **Cold homogenization** \(^{22,23}\)

Like the hot homogenization method, the drug is dissolved in the lipid melt, and then rapidly cooled by liquid nitrogen or dry ice. Milling leads to formation of nanoparticles in the range of 50-100 nm which are dispersible in a cold surfactant phase that form a pre-suspension. PHP is done at ambient temperature that leads to break the nanoparticles to NLCs. Cold homogenization technique has been expanded to resolve the problems of the hot homogenization technique \(^{1,2}\). Schematic diagram of this method is given in Figure 2.

![Figure 2: Hot homogenization and cold homogenization method.](image)

2. **Ultrasonication or high speed homogenization** \(^{24,25}\)

NLCs were also developed by high speed stirring or sonication. A most advantages are that, equipment whatever use here is very common in every lab. The problem of this method is broader particle size distribution ranging into micrometer range. This lead physical instability like particle growth upon storage. Potential metal contamination due to ultrasonication is also a big problem in this method. So for making a stable formulation, studies have been performed by various research groups that high speed stirring and ultrasonication are used combined and performed at high temperature. Schematic diagram of this method is given in Figure 3.

![Figure 3: Ultrasonication](image)
3. **Microemulsion** 26-29

This method is based on the dilution of microemulsions. As micro-emulsions are two-phase systems composed of an inner and outer phase (e.g. o/w microemulsions). They are made by stirring an optically transparent mixture at 65-70°C, which typically composed of a low melting fatty acid (e.g. stearic acid), an emulsifier (e.g. polysorbate 20), co-emulsifiers (e.g. butanol) and water. The hot microemulsion is dispersed in cold water (2-3°C) under stirring. NLCs dispersion can be used as granulation fluid for transferring in to solid product (tablets, pellets) by granulation process, but in case of low particle content much of water needs to be removed. High-temperature gradients facilitate rapid lipid crystallization and prevent aggregation.

![Figure 4: Microemulsion Method.](image)

4. **Phase inversion method** 30: In this method, fine dispersion is obtained by chemical energy resulting of phase transitions produced by emulsification pathway. The phase transition is produced by varying the composition of the emulsion and keeping temperature constant or vice versa. The phase inversion temperature was first done by Shinoda et al. it was concluded that increase in temperature results in the chemical changes of polyoxyethelene surfactants by degradation of the polymer chain with the temperature.

5. **Solvent Evaporation Technique** 31, 32

This is a method analogous to the production of NLCs solvent evaporation in o/w emulsions via precipitation. In the solvent emulsification-evaporation the lipid is dissolved in a water-immiscible organic solvent (e.g. toluene, chloroform) which is then emulsified in an aqueous phase before evaporation of the solvent under condition of reduced pressure. The lipid precipitates upon evaporation of the solvent thus forming nanoparticles.

Firstly, an organic phase has produced containing the lipid material dissolved in a water-immiscible organic solvent, and then the drug is dissolved or dispersed in that solution. This organic phase is emulsified in an o/w surfactant containing aqueous phase by mechanical stirring. Subsequent quick removal of solvent by evaporation from the obtained o/w emulsion under mechanical stirring or reduced pressure nanoparticle dispersion is formed by precipitation of the lipid in the aqueous medium. The solvent evaporation step must be quickly in order to avoid particle aggregation.

This method is suitable for the incorporation of highly thermolabile drugs due to avoidance of heat during the preparation but presence of solvent residues in the final dispersion may create problems due to regulatory concern. Limited solubility of lipids in organic materials generally leads to dilute dispersions and need to concentrate by means of another process such as ultra-filtration, evaporation or lyophilization. On the other hand small particle size around 100 nm with narrow size distribution can be achieved by this method. This procedure has schematically depicted in Fig no.5.
6. Double emulsion technique\textsuperscript{33}
In double emulsion technique used for preparation NLCs. In this the drug (mainly hydrophilic drugs) was dissolved in aqueous solution, and then was emulsified in melted lipid. This primary emulsion was stabilized by adding stabilizer (e.g. gelatin, poloxamer-407). Then this stabilized primary emulsion was dispersed in aqueous phase containing hydrophilic emulsifier (e.g. PVA). Thereafter, the double emulsion was stirred and was isolated by filtration. Double emulsion technique avoids the necessity to melt the lipid for the preparation of peptide-loaded lipid nanoparticles and the surface of the nanoparticles could be modified in order to sterically stabilize them by means of the incorporation of a lipid/-PEG derivative. Sterical stabilization significantly improved the resistance of these colloidal systems in the gastrointestinal fluids. This technique is mainly used to encapsulate hydrophilic drug (peptides).

7. Solvent emulsification-diffusion method\textsuperscript{34}
NLCs can also be produced by solvent emulsification-diffusion technique. The mean particle size depends upon lipid concentration in the organic phase and the emulsifier used. Particles with average diameters of 30-100 nm can be obtained by this technique. Avoidance of heat during the preparation is the most important advantage of this technique. Here, the lipid matrix is dissolved in water-immiscible organic solvent followed by emulsification in an aqueous phase. The solvent is evaporated under reduced pressure resulting in nanoparticles dispersion formed by precipitation of the lipid in aqueous medium.

8. Spontaneous Emulsification\textsuperscript{35}
It involves three main steps:
i. Preparation of homogeneous organic solution composed of oil and lipophilic surfactant in water miscible solvent and hydrophilic surfactant.
ii. The organic phase was injected in the aqueous phase under magnetic stirring the o/w emulsion was formed.
iii. The water-miscible solvent was removed by evaporation under reduced pressure.

9. Microfluidization\textsuperscript{36}
Microfluidization is a mixing technique, which makes use of a device called microfluidizer. This device uses a high-pressure positive displacement pump (500 to 20000psi), which forces the product through the interaction chamber, which consists of small channels called „microchannels“. The product flows through the microchannels on to an impingement area resulting in very fine particles of sub-micron range.

The two solutions (aqueous phase and oily phase) are combined together and processed in an inline homogenizer to yield a coarse emulsion. The coarse emulsion is into a microfluidizer where it is further processed to obtain a stable nanoemulsion. The coarse emulsion is passed through the interaction chamber microfluidizer repeatedly until desired particle size is obtained. The bulk emulsion is then filtered through a filter under nitrogen to
remove large droplets resulting in a uniform nanoemulsion.

7. Hydrogel Method

It is similar to solvent evaporation method. The only difference between the two methods is that the drug solvent is miscible with the drug anti-solvent. Higher shear force prevent crystal growth and Ostwald ripening.

REFERENCES


