EUROPEAN JOURNAL OF BIOMEDICAL AND PHARMACEUTICAL SCIENCES
http://www.ejbps.com

ISSN 2349-8870
Volume: 4
Issue: 10
162-167
Year: 2017

NANOSTRUCTURED LIPID CARRIER: A NOVEL APPROACH

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Article Received on 31/07/2017 **Article Revised on 21/08/2017** **Article Accepted on 11/09/2017**

ABSTRACT
The primary and foremost aim of writing this article is to focus on the importance and benefits of Nanostructured Lipid Carrier loaded drug delivery systems. The drug can be effectively distributed in the body by following various mechanism and there are also some limitations of conventional dosage forms like poor solubility, absorption, first pass metabolism and poor bioavailability, hence need for this nano structured based drug delivery systems was developed. This technique is effective to overcome the above mentioned drawbacks and also this helps us in reducing the systemic side effects, dose and dosing frequency. The most important action is the site specificity. Since there are various types of nano carriers among those SLN is effective for incorporation of hydrophilic drugs into it. But there are several disadvantages making the drug delivery less effective. The different route of administration is as like oral, topical, transdermal, ocular, rectal, vaginal, parenteral, sublingual etc. This review outlines the various parameter involved in preparation, evaluation and development of NLC's an effective drug carrier and by giving the wide pharmaceutical and industrial application.

KEYWORDS: Nanostructured lipid carrier, SLN, Bioavability, Conventional dosage system.

1. INTRODUCTION
The NLC drug delivery system is a type of the colloidal drug delivery in which the solid lipid and liquid lipid are used, providing the advantage of improving the drug loading capacity and release kinetics. The technique generally emphasizes on the increased solubility and bioavailability of the drug moieties. Since there are various routes of the drug administration such as oral, nasal, ocular, rectal, vaginal, parenteral, topical etc. in this technique there is aqueous dispersion of the solid nanoparticle, composed of a mixture of solid and liquid lipids, and stabilized by one or two surfactant. NLC's usually fall under the diameter ranging from 10-1000nm. NLC's usually overcome the limitation of the SLN such as high payload, expulsion of the drug during storage, high entrapment efficiency, high water content of SLN dispersion. The various problem of the dermal layer can be overcome e.g. low uptake due to the barrier function of the stratum cornea and absorption to the systemic circulation. The scientific articles state the delivery of the API's effectively across the skin layer. These include reservoir matrices, matrix diffusion-controlled devices, multiple polymer devices and multilayer matrix assemblies. SLN and NLC are composed of physiological and biodegradable lipids that show low toxicity. Due to the occlusive properties of lipid nanoparticles, an increased skin hydration effect is observed. Furthermore, lipid nanoparticles are able to enhance the chemical stability of compounds sensitive to light, oxidation and hydrolysis.[1,2,3]

2. NANOPARTICLES[2]
Nanoparticles are colloidal drug delivery system, basically sub-nano sized. The system is composed of the synthetic or semisynthetic polymers. Size range varies from 10nm to 100nm. The drug is dissolved, entrapped or attached to the polymeric matrix structure. The solid, lipid drug particles can be entrapped effectively into the matrix.

2.1 Types of Nanoparticles

There are several types of Nano particulate drug delivery as follows:

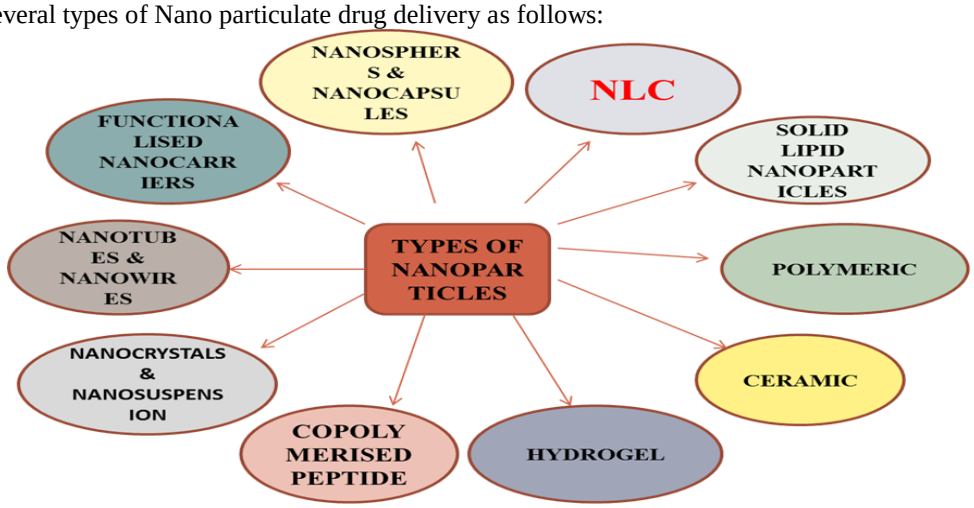


Figure 1: Types of Nanoparticles.

3. WHY TO SELECT THE LIPID NANOPARTICLES?

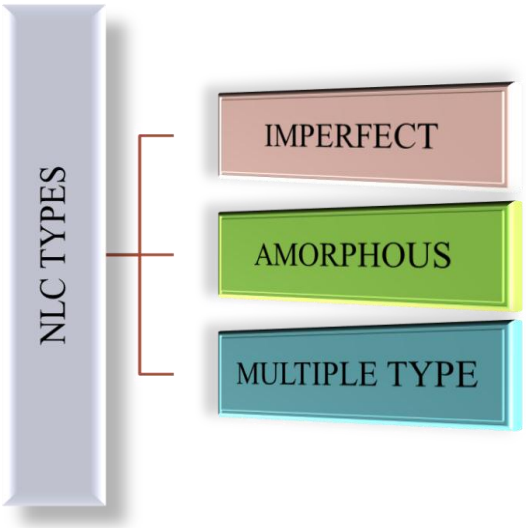
- Shows good control of the release kinetics of encapsulated drug.
- Increased bioavailability of the entrapped moiety.
- Protection of the labile drug moiety.
- Relatively easy to manufacture the bio polymeric nanoparticles.
- Wide solvent range and base material.
- Shows long term stability report.
- Conventional manufacturing method is applicable.
- Wide range of application.

4. ADVANTAGE OF NLC OVER CONVENTIONAL CARRIERS SYSTEMS[4,5]

- Site-specific drug delivery system.
- Controlled and sustain release.
- Drug protection against the biochemical degradation.
- High drug holding capacity.
- Lipophilic and hydrophilic drugs can be incorporated.
- Steam and radiation sterilization possible.
- Lyophilization and spray drying possible.
- Cheap and stable.

5. TYPES OF NLC[6,7]

There are 3 types:



The problems of the SLN is the formation of the perfect crystal shape so which in turn result into dense compact molecule. There is requirement of the imperfect nature of the substance so that large amount of the drug can be incorporated. The drug load of the SLN is less due to the formation of lipid crystals. Crystallization process if avoided these can lead to the elimination of these problems. The lipid matrix should be solid and in

amorphous state. The NMR and DSC technique can be performed to determine the solid character.

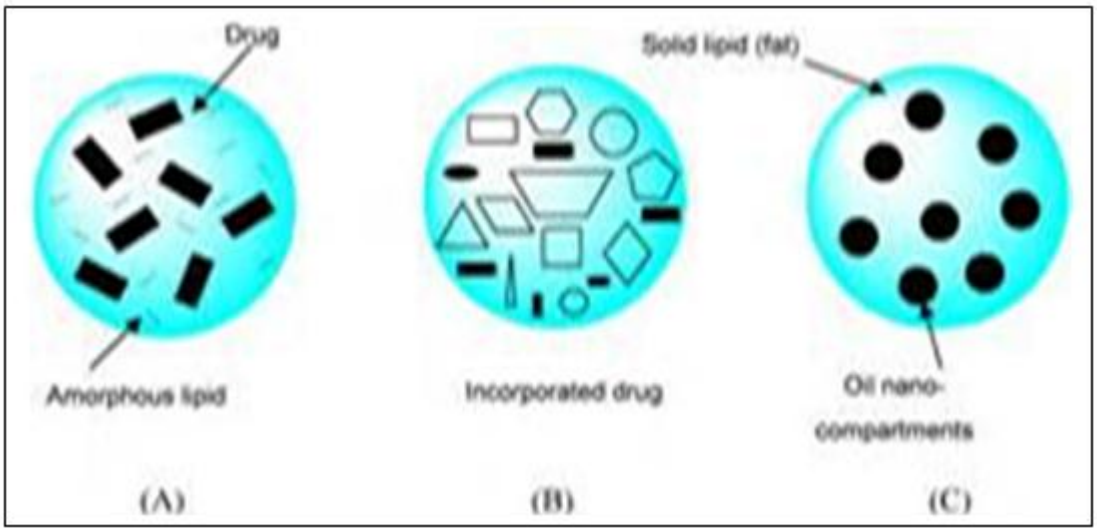


Figure 3: (A) The Multiple type, (B) The Imperfect type, (C) The Perfect type.

6. POTENTIAL BENEFITS OF THE NLC

- **Skin occlusion**[8,9,10,11]

The lipid film formation on the skin surface resulted in to occlusive effect due to the nanoparticles. The nano size of the drug formulation and also having crystalline nature with low melting point and also particles size less than 400nm and containing at least 35% lipid is very effective. Comparative result of the NLC with conventional formulation having high oil content showed decrease in the occlusion.

- **Skin hydration and elasticity**[12]

The occlusive effect causes the decrease in the total epidermal water loss (TEWL) and which in turn increase the skin hydration. An *in vivo* study showed that the NLC containing O/W cream increased the skin hydration significantly than conventional O/W cream. In study shows that the skin hydration effect after repetitive application of an O/W cream containing SLN and a conventional O/W cream was investigated for 28 days.

- **Enhancement of the skin permeation and drug targeting**[13,14,15]

In healthy skin stratum cornea has typically a water content of 20% and provides relatively an effective barrier against percutaneous absorption of exogenous substances. Skin hydration after applying NLC leads to a reduction of corneocytes packing and an increase in the size of the corneocytes gaps. This will facilitate the percutaneous absorption and drug penetration to the deeper skin layers.

- **Enhancement of chemical stability of chemically labile compounds**[16,17,18,19]

Enhancement of chemical stability after incorporation into lipid Nano carriers was proven for many cosmetic actives e.g. coenzyme Q 10, ascorbyl palmitate, tocopherol (vitamin E) and retinol (vitamin A).

- **Enhancement of UV blocking ability**[20,21]

The UV rays which fall on the body surface is harmful thus leads to various complication. This ray generally causes the skin irritation, allergic reactions and skin cancer. The UV B is very harmful among all. The benzophenon can be used and *in vitro* studies can be performed. Improving the UV blocking activity by incorporation of the UV blockers, the SPF upto 50 was reported after encapsulation of tritanium dioxide into NLC.

7. METHOD OF PREPARATION OF NLC

There are various method employed in the preparation of NLC as follows:

1. High-Shear Homogenization and Ultrasound

High shear homogenization and ultrasound anciently used to produce the lipid Nano particulate dispersion. This method has wide application range and easy accessibility. Micrometer size range particles are produced. Average particle sizes in the range of 100 to 200 nm were obtained using stirring rates of 20,000 to 25,000 rpm for 8 to 10 min and controlled cooling with a stirring rate of 5,000 rpm. In addition, metal contamination has to be considered if ultrasound is used a rotor-stator homogenizer to produce SLN/NLC by melt-emulsification.[27,28]

2. High Pressure Homogenization

High Pressure Homogenization Technique has been proved as a powerful tool for the large scale production of NLC's, lipid drug conjugate, SLN's and parenteral emulsions. In this technique high pressure i.e. 100-200bars is generally used. The lipid is passed through the narrow gap of few micron ranges. Shear stress and cavitation force which leads to disruption of particle. Generally the lipid content is in the range of 5-10%. Basically there are two important types hot and cold

homogenization techniques. In both the technique drug is dissolved in the lipid being melted at approximately 510^0 C above the melting point.[29,30]

2.1 Hot Homogenization

Hot homogenization technique is carried out at temperature above the melting point of the lipid. The emulsion is prepared in the series firstly pre emulsion is prepared then the emulsion. In pre emulsion the drug is mixed with the lipid further melting was carried out, aqueous emulsifier phase is obtained by using the high shear homogenization technique. Increase in the temperature here is decrease in the viscosity of inner phase and particle size. But this further leads to the degradation of the drug moiety and labile substances. The use of several surfactants has decreased solubility and HLB values at a higher temperature, which might have a negative impact on homogenization efficacy. The technique increase the temperature 10^0C for every 500bar pressure, 3 to 5 homogenization cycles at 500 to 1500 bar are sufficient. The primary product of the hot homogenization is a nano emulsion resulting from the liquid state of the lipid. Solid particles are formed by the cooling of the sample to room temperature or below.[29,30]

2.2 Cold Homogenization

Cold homogenization is also referred as a high pressure milling of a lipid suspension. The process is carried out on the solid lipid particles. It should be ensure that the un-molten state of the lipid should be preserved due to rise in the temperature during the homogenization process.

- There is no temperature effect on the drug and no further degradation.
- Even drug distribution into the aqueous phase.
- No complexity of the crystallization step.[29,30]

3. SLN/NLC Prepared by Solvent Emulsification/Evaporation

The solvent evaporation method is simple method for the preparation of the NLC/SLN. In this technique the lipid phase is dissolved into the aqueous phase which leads to the formation of the oil/water (O/W) emulsion. When the pressure is reduced solid lipid nanoparticle dispersion is formed. Mean particle sizes of the final particles ranged from 30 to 100 nm, depending on the lecithin/co-surfactant blend. There is no thermal stress employed in the method. But the method has disadvantages of organic solvent.[31,32]

4. Micro Emulsion-Based SLN/NLC Preparations

In this concept there two phase system is generally produced i.e. inner and outer phase (e.g., o/w micro emulsions). There is stirring at 65 to 70^0C. the low-melting fatty acid mixture is optically transparent. Fatty acid used are stearic acid, oleic acid, tristearin, cholesterol, cetyl palmitate etc. an emulsifier used are polysorbate 60, polysorbate 20 etc. co-emulsifiers like butenol, sodium monoctylphosphate.[33]

8. CHARACTERIZATION OF NLC[34,35,36,37]

1. Particle Size

Photon correction spectroscopy (PCS): The technique can be performed by taking the triplicate reading and further standard deviation is calculated. PCS is based on laser light diffraction provides an appropriate method for investigation and can be applied for particles ranging below 200 nm and up to 1µm 86. For particles below 200nm Rayleigh's theory holds that the scattering intensity to be proportional to the sixth potency of the particle diameter.

2. Scanning Electron Microscopy (SEM)

This method is generally used to determine the particle size and shape of the formulation. The technique can be performed by using the NLC dispersion and then spread on a suitable sample holder. There is use of the electron gun which is placed on the microscope, vacuum condition is maintained by pumping the air out of the medium and sample is placed in this chamber. The beam of the electrons is then passed. This beam is of high energy primary electrons. The emitted electrons concentrate on the specimen and scan the particles. As the focused electron beam hits the particles the ionization process takes place and converted into secondary electrons. The lateral collector is used to collect the electron and signal is amplified.

3. Zeta Potential

The zeta potential difference existing between the surface of a solid particle immersed in a conducting liquid and bulk liquiud. it cannot be directly calculated hence, theoretical or estimated experimentally often based on electrophoretic mobility. Basically to determine zeta potential one tracks that rate at which a charged particle moves in response to an electric field.

4. Differential scanning calorimetry (DSC)

The concept generally focused on the Heat Flux mechanism. The technique the generally determine the physical and energetic properties of a formulation. It measures the heat loss or gain in a system as a result, physical or chemical change within a sample. There are 2 types of the system, the power compensated and heat-flux DSC.

5. X-ray Scattering

The physical appearance of the particle, its crystal lattice design can be stated by using the X-ray diffraction technique. There is the geometric scattering of the radiation from the crystal planes of the formulation. It states the degree of crystallinity in the formulation. Lyophilized compounds can be detected by this method. The powdered samples of lipid, drug and lyophilized NLC were placed on the top of X-ray plates.

6. Drug Release

The release pattern of the drug very important in to determine whether the formulation is showing the sustained, prolonged or controlled release. The

controlled and sustained release formulation of NLC shows the increased half-life and retards the enzymatic action in the circulatory system. Sustain release of the drug is function of the interfacial membrane and partition between the lipid matrix and water.

7. Drug entrapment efficiency

In this technique the percentage of the drug entrapped into the polymeric matrix and present in solvent is determined. The method can be performed as follows:
The suitable drug is dissolved in solvent. Further it is centrifuge at 12500rpm for 45min so that the two layers will get separated i.e. lipid and aqueous phase, then the supernatant is diluted with solvent and filter through 40µm filter paper and determined by UV spectrometer. The % entrapment efficiency can be calculated.

9. APPLICATION OF NLC[38]

- There are wide range of application are as follows:
- Topical drug delivery
- Oral drug delivery
- Brain targeted drug delivery
- Pulmonary drug delivery
- Chemotherapy
- Cardiovascular drug delivery system
- Cosmetic application
- Ocular drug delivery system

CONCLUSION

The nanostructured lipid carrier is one of the most important techniques used to deliver the drug. The technique enhances the bioavailability of the poorly soluble drugs. Also increase the penetration into the skin, hence increasing treatment efficiency, target the epidermis and reduce systemic absorption and side effects. The present findings also state the information NLC's are useful in delivering the drug to targeted site, at predetermined time and concentration. This technique provides flexibility in drug loading, modulation of release and problem of drug expulsion. The method is relatively cost effective by providing the encapsulation for the irritant drugs, minimizing the side effect. It also gives wide range of application in the potent drugs delivery in the cancer treatment. There is continued effort to increase the application of the NLC's in pharmaceutical industry. Providing flexibility for large scale preparation of the formulations hence has a lot of potential in the coming years in various fields.

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