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NANOSTRUCTURED LIPID CARRIERS- A REVIEW

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ABSTRACT

Lipid nanoparticles (LNPs) have gained attention during last few decades due to several advantages. Lipid nanoparticles are classified into two namely Solid lipid nanoparticles (SLNs) and Nanostructured lipid carriers (NLCs). SLNs such as liposomes, polymeric nanoparticles and emulsions were developed for improved stability, better release profile and delivery at targeted site. Nanostructured lipid carriers (NLC) are next generation lipid nanoparticles, are generally referred to as modified solid lipid nanoparticles (SLNs). NLC are mixture of solid and liquid lipids that results in partial crystallized lipid system and imparts numerous advantages over other solid lipid nanoparticles which includes flexibility in drug release, higher stability and improved drug loading capacity. The concept of NLCs can be easily applied in pharmaceutical industries and laboratories due to its ease and cost effective manufacturing, biocompatibility, non-toxicity, ease of delivery at target site/ site specific delivery via several routes of administration. This review highlights the advantages, types, structure, and method of fabrication for stable formulation and application of NLC in pharmaceutical field. An overview of reviews was conducted to locate published literature between 2000 and 2020.

KEYWORDS: Nanostructured lipid, NLC, Nanoparticles, solid lipid nanoparticles, controlled release, bioavailability enhancers, colloidal drug carrier.

INTRODUCTION

Nanoparticles are colloidal particles with approximate size of 10 –1000 nm.[1] These particles are usually classified into two namely, nanocarriers and nanodrugs. The nanocarriers are material prepared by drug dispersion or dissolution with polymers and or, lipid materials.[2] The nanocarriers formed are classified as either nanospheres or nanocapsules.[3] The formulations prepared with polymeric material are referred to as PNP, and it includes

polymer nanocapsules and nanospheres as well as polymeric micelles. Similarly, a formulation prepared by lipid material is referred to as lipid nanoparticle, and includes nanoliposomes and NLCs. Although, a new form of nanocarriers has also been explored, this is the combination of liposomes and polymers and referred to as LPN.

NLCs, as a lipid based drug delivery system gained attention in last decade mainly in 1990's.[4] NLCs are basically modification of Solid Lipid Nanoparticles, the binary mixture of solid and liquid lipids formulated by heating and cooling crystallization. The size of NLCs varies in the range 10-500 nm.[5] The mixture NLC's consist of long chain liquid and lipid and short chain solid and lipid having ratio of 99.9: 0.1 and 70:30 respectively.[6] The approach of NLCs got consideration because of the advantages such as prevention of drug leakage, high drug loading efficiency, biodegradable carrier material, lower side effects, lesser *in vitro* toxicity, targeted delivery or site specific delivery and stability.[7] NLCs can be useful for both hydrophobic and hydrophilic drugs with higher drug loading capacity.[8] As the NLCs are composed of solid and liquid lipids they can accommodate more drug content as compared to SLN. NLCs are solid at room temperature even in the presence of liquid lipids. NLCs can more strongly immobilize drugs and prevent the particle from coalescing by virtue of the solid matrix compared to emulsions.[9] NLCs have wide applications in pharmaceuticals for oral, ocular, parenteral, pulmonary, topical and transdermal route. The concept of NLCs has been applied in chemotherapy, gene therapy, cosmeceuticals, nutraceuticals and food industries etc.[9,10]

As per Müller et al., the NLC are structurally classified into 3 types based on the location of the drug moieties namely, NLC Type I (Imperfect crystal model), NLC Type II (Multiple type), NLC Type III (Amorphous model).[1,11]

NLC type I (Imperfect crystal model)

As the name indicates, NLC type I consist of badly or highly distorted structures with spacious cavities that can hold high amount of drug molecules. These imperfections are observed as it consists of solid lipids with high amount of liquid lipids such as mono, di and triglycerides. Although this matrix increases drug payload but has limited drug entrapment efficiency.[11,12]

NLC Type II (Multiple type)

NLC type II consists of oil, lipid and water phase making it "Multiple Type NLC". It is actually oil-in-lipid-in-water type. It is similar to that of the water-in-oil-in-water (W/O/W) microemulsions. The concept of multiple type was lead for the hydrophobic drugs because of their inherited character of high solubility in liquid lipids. And hence, NLC type II was developed using high amount of liquid lipids. At low concentration, oil moieties can easily disperse in lipid matrix. Further addition of oil induces phase separation forming small oily nano compartments incorporated in solid lipid matrix. NLC type II can offer several advantages such as higher drug entrapment, controlled release of drug and minimal drug leakage.[11-13]

NLC type III (amorphous model)

The concept of NLC type III was approached in order to prevent drug leakage due to process of crystallization. In this technique, the lipids are carefully mixed to minimize drug leakage. The mixture of lipids remain solid but in homogenous amorphous state. Hence, they are called Amorphous type NLC. Various lipids are used in formulation and these include hydroxyl octacosanyl, hydroxyl stearate, isopropyl palmitate, isopropyl myristate or dibutyl adipate. The NLC so prepared exist in solid but non-crystalline amorphous state.[13,14]

Advantages of Nanostructured Lipid Carriers[15-25]

Improved stability

Excellent biocompatibility

No use of organic solvents as it is water based system

Low cost as compared to other carrier system

Biodegradable

Ease of preparation

Increased dispersion in aqueous medium

Higher drug entrapment capacity (Hydrophilic and Lipophilic drug)

Controlled Particle size

Improved efficiency carrier for lipophilic drugs

Higher skin permeation

Controlled release of drug

Prevent burst release of drug

Optimum carrier for topical drug as all the excipients used in topical preparations are approved

Enhanced stability of drugs

Improved benefit/risk ratio

Disadvantages of Nanostructured Lipid Carriers[7,26]

High content of surfactants may cause discomfort, irritation and sensitization

May cause cell damage

Inadequate reports of preclinical and clinical studies with these nanoparticles in case of bone repair

Stability of Lipids

Growth of particle size

Components of NLC

The NLC are composed of solid and liquid lipids, surfactants and water. The solid lipids and oil are mixed in the ratio of 70:30 and 99.9:0.1. The surfactant is used as stabilizer in 0.5 to 5% concentration.[27]

Solid Lipids

The solid lipids for the preparation of NLC are selected on the basis of dissolution of drug. A combination of several chemical compounds having melting point higher than 40^{o}C are usually preferred. Solid lipids having high tolerability in human use and biodegradable are most preferable.[28] The drug is mixed in increasing quantities in molten solid lipid and the highest quantity of drug is determined where it has completely dissolved in solid lipid. Most commonly used lipids are Stearic acid, palmitic acid, beeswax, carnauba wax, dynasan, precifac, theobroma oil, Hydrogenated palm oil, trilaurin, trimyristin Tristearin, tripalmitin, tribehenate, Glyceryl Monostearate and Mixture of glyceryl mono, di and tribehenate Medium-chain triglycerides caprylic/capric.[29-31]

Liquid Lipids

The liquid lipids for NLC are selected on the basis of solubility of the drug. The liquid lipids having high tolerability in human use and biodegradable are most preferable. Most commonly used lipids are Cetiol V, miglyol, castor oil, oleic acid, davana oil, palm oil, olive oil and propylene glycol dicaprylate/caprate etc.[32]

Surfactants

The surfactants are used as stabilizers in NLCs. They depend upon surfactant HLB and molecular weight. The surfactant affinity for the various lipids also differs. Based upon the HLB and surfactant affinity, suitable surfactants should be selected. Mostly commonly used surfactants are poloxamer-188, tween 80, egg lecithin, soya lecithin, Polysorbate 20, Polysorbate 80, Cremophor EL, Solutol HS, Tego Care 450, Span 65.[33]

Method of Preparation of NLC

Numerous methods are used to fabricate NLC and these include High pressure homogenization method, Microemulsion method, Solvent diffusion method, Solvent emulsification evaporation method, emulsification sonication method, phase inversion technique, Solvent displacement method, and membrane contractor technique.[5,34,35]

1. **High-pressure homogenization:** The high-pressure homogenization can be either hot homogenization or cold homogenization. In this technique, the particles of stable emulsion are subdivided to nano size. Two types of homogenizers are commonly used: jet-stream homogenizers, piston-gap homogenizers.[36]

a. **Hot homogenization:** This process is executed at a temperature above melting point of lipids. In this method, lipids (solid and liquid) are melted and mixed with the drug and surfactant (stabilizer). The temperature is maintained constant throughout the process. The above prepared emulsion is then homogenized at high pressure (3 to 5 cycles at 500-1500 bar). During cooling, the emulsion is formed and re-crystallized to form NLC.[37]

Advantage: Simple and economical method.

Disadvantage: Temperature may rise during the process.

b. **Cold Homogenization:** In this process, the drug is mixed with melted solid and liquid lipids. The drug-loaded lipids are then solidified using dry ice and milled to nano size quickly. The particles are distributed in a relatively cool surfactant solution prior to applying it to high pressure homogenization (5 to 10 cycles at 1500 bar) at or below ambient temperature.[38-41]

Advantage: Feasibility of large-scale production, No organic solvent in the formulation, Useful for thermolabile drugs.

Disadvantage: Presence of microparticles along with NLC.

2. **Microemulsion:** In this process, the drug is dissolved in melted form of solid and liquid lipids. This mixture is then emulsified with hot surfactant solution. The microemulsion is poured in cold water with constant stirring to obtain nanoemulsion. It is then recrystallised to form NLC.

Advantage: Large scale production.

Disadvantage: Uses a high percentage of surfactants that may lead to irritation and sensitization.[42]

3. **Solvent Diffusion method:** The solid and liquid lipids are dissolved in organic solvent and dispersed in water with constant stirring. The cooling while stirring results in solidification of lipids. Commonly used organic solvents are tetrahydrofuran and benzyl alcohol.

Advantage: Use of water immiscible solvents.[43]

Disadvantage: Requires lyophilisation for stability.

4. **Solvent Emulsification Evaporation Method:** In this method, the solid and liquid lipids are dissolved with water immiscible solvent and dispersed in aqueous solution of emulsifiers to produce o/w emulsion. This mixture is then evaporated under reduced pressure in order to form dispersion of nanoparticles in aqueous phase by precipitation of lipid. Particle size so obtained is 30-100 nm. The organic solvent used is cyclohexane and chloroform.

Advantage: Suitable for thermo-sensitive drugs.

Disadvantages: Use of water-immiscible solvents, Evaporation of the organic phase required.

5. **Emulsification Sonication Method/ Ultrasonication method:** In this method, the solid and liquid lipids are mixed with drug (oil phase) and dispersed in surfactant solution (aqueous phase) using probe Sonicator for ultrasonication. The mixture is then cooled and solidified to form NLC. This stable emulsion is heated under reduced pressure to evaporate the oil phase by constant stirring.[44-46]

Advantage: Excellent shear mixing.

Disadvantage: Metal contamination may occur by probe.

6. **Phase Inversion Technique:** In this method, the solid and liquid lipids are blended along with medicament, water, and surfactant (stabilizers) with constant stirring and passed through heating and cooling cycle (85-60-85°C). Thereafter, the mixture is cooled by

diluting with cold water (0°C) and this phase inversion results in the formulation of NLC.[42,44]

Advantage: Used for heat sensitive medicaments, No utilization of the organic phase.

Disadvantage: Tedious process.

7. **Solvent Displacement Method:** In this method, the solid and liquid lipids are mixed in an organic solvent. This mixture is then quickly added/ injected to surfactant solution (stabilizers) with the help of a needle. This mixture is then dried and NLC are obtained.

Advantage: Fast process.

Disadvantage: Use of water-immiscible solvents.[42]

8. **Membrane Contractor Technique:** In this method, solid and liquid lipids are melted and passed through porous membrane to obtain minute liquid droplets. Along with this, water is also circulated that passes the lipid droplets outside the pores easily. The droplets are then cooled at optimum temperature to form NLC.

Advantage: Easiest method.[47]

9. **Spray Drying:** In this method, the solid and liquid lipids are melted and blended with medicaments and surfactant (stabilizers). This mixture is then spray dried to form NLC. The solid lipids with melting point higher than 70^{o}C are used in the preparation of NLCs. Advantage: More economic and efficient method.

Disadvantage: Risk of particle aggregation, degradation of lipids due to high melting point.[48-52]

10. **Microfluidics:** In this method, liquid lipids are passed through microfludics chips at controlled flow rate. This leads to collision and rapid mixing of lipids at controlled pressure. The mixture is then cooled and solidified to form NLC at room temperature.

Advantage: Minimizes polydispersity, Less time consuming, no use of organic solvents.[53-55]

Applications of NLC

NLCs have been used from last few decades as it has potential application in various fields. The applications of NLC are divided in two broader aspects covering the therapeutic applications which include the various routes of administrations in drug delivery and the second part describes the applications in other fields including cosmetics, nutraceuticals, food, chemotherapy and gene delivery. These are discussed below:

Therapeutic applications

Topical delivery: NLC has been widely used for topical route for their unique properties. NLCs can enhance the apparent solubility of entrapped drugs, which can form high concentration gradient on skin to facilitate drug permeation. The NLC can adhere to skin surface and control the drug release.[42]

Oral delivery: NLCs can be used for oral delivery of poorly water soluble drugs having low bioavailability. Oral NLC can enhance drug loading capacity, patient compliance, increase intestinal permeability and decreased degradation and clearance. They can also adhere to gut wall and enhance absorption.[56,57]

Parenteral delivery: NLC have been widely used for parenteral delivery of hydrophobic drugs. They can be easily manufactured, have high drug loading capacity, controlled release of drugs, and biocompatibility of the excipients for intravenous delivery of the drug with passive targeting ability and easy abolishment.[42]

Ocular drug delivery: Adding permeation enhancers to the NLC for ophthalmic drug delivery can be a potential approach for the treatment of ocular diseases and disorders. NLC can increase the ocular bioavailability of hydrophobic drugs.

Drug delivery to brain: Drug delivery to the brain can effectively reduce the number of doses and side effects and avoids the first pass metabolism. NLC for brain delivery includes no modification of drug molecules as the drug can be rapidly uptake by brain, bio acceptability and biodegradability.

Pulmonary drug delivery: Drug delivery via inhalation is also a potential route for the treatment of several pulmonary disorders having advantages over conventional (parenteral and oral) dosage forms like a) non-invasive b) circumventing first pass metabolism and systemic toxicity c) reduced frequent dosing and d) site specificity by directly reaching to the lung epithelium thereby enhancing local drug concentrations.[58,59]

Other applications

NLC have a vast potential in cosmeceuticals and can be used in various forms such as gel, cream, lotion, ointment. The beneficial aspects associated with these NLCs in cosmeceuticals are very broad which lies in, enhancing skin bioavailability of active ingredients, film formation and controlled occlusion, UV protection, penetration enhancement and epidermal

targeting, enhancement of physical and chemical stability and in vivo skin hydration. NLC as nutraceuticals can provide medicinal or health benefits, including the prevention, and treatment of diseases. Among them, the carotenoids are one of the most important groups of natural pigments, because of their wide distribution in plant tissues, structural diversity and numerous functions.[42]

CONCLUSION

The lipid nanoparticles like NLC have gained attention for its good therapeutic and cosmeceuticals applications and have bright future prospects. The carrier system is very useful for both hydrophobic and hydrophilic drugs with enhanced drug loading, drug absorption through intestine, permeation through skin and controlled and sustained release profile. This review mainly focused on the role of NLCs as novel carrier system for numerous drugs. The modification in the surface and core of the nanostructured lipids can even be more beneficial for enhancing the drug loading and solubilization capacity.

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