**Nanostructured lipid carrier (NLC) as recent drug carrier; Review Article**

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Abstract

Nanostructured lipid carriers (NLCs) are drug-delivery systems composed of both solid and liquid lipids as a core matrix. It was shown that NLCs reveal some advantages for drug therapy over conventional carriers, including increased solubility, the ability to enhance storage stability, improved permeability and bioavailability, reduced adverse effect, prolonged half-life, and tissue-targeted delivery. NLCs have attracted increasing attention in recent years. This review describes the structures, preparation techniques, and application of NLCs are systematically elucidated in this review. The potential of NLCs to be used for different administration routes is highlighted. Relevant issues for the introduction of NLCs to market, including pharmaceutical and cosmetic applications, are discussed.

Introduction

Nowadays number of new drug molecules developed, but about 40% of new drug candidates identified by chemical screening as poorly water solubility and low bioavailability. There is a need to develop a drug delivery systems which overcome these problems. As an alternative system to emulsion, liposomes (1) and polymeric micro particulate systems, Lipid nanoparticles (Solid lipid nanoparticles (SLN) and Nanostructured lipid carrier (NLC) has developed due to their own limitations. SLN gained lot of popularity among researcher due to its applicability for various routes such as oral, parenteral, topical and also the properties of site specific and controlled drug delivery with reduced side effects. Along with their advantages, some challenges such as low drug loading, drug expulsion from SLN during storage and high water content of SLN dispersion. These limitations were overcome in nanostructured lipid carriers (NLC), which are second generation the new type of Lipid nanoparticles, based on mixture of solid lipids with spatially incompatible liquid. They offer the advantage of improved drug loading capacity and release properties of poorly soluble drug mainly due their imperfect or unordedred structure. They may increase, bioavailability and stability of bioactive compounds, and shelf-life, functionality, consumer acceptability, nutritional value and safety of food systems, and provide controlled release of encapsulated materials. The lipid-based NLCs system was developed to overcome the limitations of SLNs, such as drug loading into a solid matrix and drug expulsion during storage because of polymorphic modification of the lipid particles. SLNs use only one form of lipid, ie, a solid lipid that orients the drug between the fatty acid chains of glycerides. In contrast, NLCs use a blend into the lymphatic system depends primarily on the size of the nanoparticles. Larger lipid nanoparticles accumulate at the injection site, and the drug is slowly released from the nanoparticles. The free drug can enter the blood circulation via pores on the walls of the capillaries. Smaller lipid nanoparticles (<0.1 µm) can easily access the lymphatic capillaries and concentrate in regional lymph nodes[1].Thus, based on these advantages, NLCs could be developed as a carrier for lymphatic drug delivery by subcutaneous administration because they have improved physicochemical properties compared with other lipid-based nanocarrier systems.

***Advantages of Nanostructured lipid carrier***

1. Control and targeted drug release.
2. Improve stability of pharmaceuticals.
3. High and enhanced drug content (compared t o other carriers).
4. Feasibilities of carrying both lipophilic and hydrophilic drugs.
5. Most lipids being biodegradable, SLNs have excellent biocompatibility.
6. Water based technology (avoid organic solvents).
7. More affordable (less expensive than polymeric/surfactant based carriers).
8. Easier to validate and gain regulatory approval[2].

 ***Disadvantages of Nanostuctured lipid carrier***

1. Cytotoxic effects related to the nature of matrix and concentration
2. Irritative and sensitising action of some surfactants,
3. Application and efficiency in case of protein and peptide drugs and gene delivery systems still need to be better exploited
4. Lack of sufficient preclinical and clinical studies with these nanoparticles in case of bone repair [3].

***Types of Nanostructured lipid carriers:***

***Type I: Highly imperfect solid matrix:***

Solid lipids and liquid lipids (oils) are blended. The difference in the structures of the lipids and special requirements in the crystallization process lead to a highly disordered, imperfect lipid matrix structure offering space for drug molecules and amorphous clusters of drugs (Figure 1, I) [4].

***Type II : Multiple oil/fat/water carrier:***

In general, drug solubility is higher in liquid lipids than in solid lipids. Based on this, particles were produced with a high content of liquid lipids (oils). At high oil concentrations a miscibility gap of the two lipids (solid lipid plus oil) occurs during the cooling phase, leading to phase separation, that means precipitation of tiny oily Nano compartments (Figure 1, II). In this multiple oil/fat/water, type II drug can be accommodated in the solid, but at increased solubility in the oily parts of the lipid matrix[4].

***Type III: Amorphous Matrix:***

Lipids are mixed in a way that prevents them from crystallizing. The lipid matrix is solid, but in an amorphous state (Figure 1, III) the absence of crystallization avoids drug expulsion by crystallization[4].



Figure 1: Different Types of Nanostuctured lipid carriers

***NLC ingredients:***

NLC are a nano-particulate carrier system derived from O/W Nano emulsions. Like nano- and micro-emulsions, the major ingredients of NLC are lipid, surface active agent and water [5].

***1. Solid Lipid :***

|  |  |
| --- | --- |
| **Hard fats** | Stearic acid, Palmitic acid, Behenic acid |
| **Natural hard fats****Triglycerides****Waxes** **Mono, di and triglycerides****mixtures** | Goat fat, Theobroma oilTrimyristin (Dynasan 114),Tripalmitin (Dynasan 116),Tristearin (Dynasan 118), TrilaurinBeeswax, Cetyl palmitate,Carnauba waxWitepsol bases, Glycerylmonostearate (Imwitor 900),Glyceryl behenate (Compritol 888ATO), Glycery palmitostearate(Precirol ATO 5), Softisan 142 andSoftisan 154[5]. |

***2. Liquid Lipid :***

Oleic acid, soya bean oil, palm oil, coconut oil, Medium chain triglycerides (MCT)/caprylic- and caprictriglycerides, Squalene, corn oil[5].

***3. Emulsifier :***

|  |  |
| --- | --- |
| **Surfactant** | **HLB** **value** (hydrophilic-lipophilic balance ) |
| **Lecithin** | **4-9** |
| **Poloxamer-188** | **29** |
| **Polysorbate 20** | **16.7** |
| **Polysorbate 80** | **15** |
| **Cremophor EL** | **12-14** |
| **Solutol HS** | **15**[5]. |

***METHODS OF PREPARATION OF NLCs:***

***High Pressure Homogenization Technique:***

 HPH has been used as a reliable and powerful technique for the large-scale production of NLCs, lipid drug conjugate, SLNs, and parenteral emulsions. In High Pressure Homogenization technique lipid are pushed with high pressure (100-200bars) through a narrow gap of few micron ranges. So shear stress and cavitation are the forces which cause the disruption of particle to submicron range. Normally the lipid contents are in the range of 5-10%. In contrast to other preparation technique High Pressure Homogenization does not show scaling up problem.Basically there are two approaches for production by high pressure homogenization, hot and cold homogenization techniques [6] . For both the techniques drug is dissolved in the lipid being melted at approximately 5- 10º C above the melting point.

***Hot Homogenization Technique:***

 In this technique the drug along with melted lipid is dispersedunder constant stirring by a high shear device in the aqueous surfactant solution of same temperature. The pre-emulsion obtained is homogenised by using a piston gap homogeniser and the obtained nanoemulsion is cooled down to room temperature where the lipid recrystallises and leads to formation of nanoparticles[7].

***Cold homogenisation technique :***

 Cold homogenisation is carried out with the solid lipid containing drug. Cold homogenisation has been developed to overcome the problems of the hot homogenisation technique such as, temperature mediated accelerated degradation of the drug payload, partitioning and hence loss of drug into the aqueous phase during homogenisation. The first step of both the cold and hot homogenisation methods is the same. In the subsequent step, the melt containing drug is cooled rapidly using ice or liquid nitrogen for distribution of drug in the lipid matrix. Cold homogenisation minimises the thermal exposure of the sample[8].

***Micro emulsion based method:***

 Melted lipid containing drug mixed with surfactant, co surfactant containing aqueous phase prepared at the same temperature as of the lipid in such a ratio to form micro emulsion. The hot micro emulsion is then diluted into excess of cold water. Sudden reduction in temperature causes breaking of the micro emulsion, converting it into Nano emulsion, which upon recrystallization of lipid phase produces lipid particles[9].

***Emulsification-Solvent Evaporation Technique :***

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 of 25 nm mean size[9].

***Solvent emulsification-diffusion method:***

The 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. In this procedure an o/w emulsion is formed comprising organic phase partially water miscible solvents (e.g. benzyl alcohol, ethyl format, tetrahydrofuran) mutually saturated with water to ensure initial thermodynamic equilibrium of both liquids (water and solvent typical ratio: 1:5–1:10) [9].

***Phase inversion method :***

 It involves two basic steps, first is addition of formulation components with magnetic stirring and subsequent heating cooling cycles and second is dilution under cooling conditions. Three cycles of heating and cooling from room temperature to 85ºC and back to 60º C are subsequently applied at a rate of 4ºC/min. This thermal treatment (85ºC-60ºC-85ºC-60ºC-85ºC) will cause the inversion of the emulsion[9].

***Melting dispersion method:***

 In melting method, drug and solid lipid are melted in an organic solvent regarded as oil phase, and simultaneously water phase is also heated to the same temperature as oil phase. Subsequently, the oil phase is added to a small volume of water phase and the resulting emulsion is stirred at high speed for few hours. Finally, it is cooled down to room temperature to yield nanoparticles[11].

***High Shear Homogenization or Ultrasonication Technique:***

 Ultrasonication based on the mechanism of cavitation. In first step, the drug was added to previously melt solid lipid. In second step, the heated aqueous phase (heated to same temperature) was added to the melted lipid and emulsified by probe sonication or by using high speed stirrer or aqueous phase added to lipid phase drop by drop followed by magnetic stirring. The obtained pre-emulsion was ultrasonicated usingprobe sonicator with water bath (at 0ºC). In order to prevent recrystalization during the process,the production temperature kept at least 5ºC above the lipid melting point. The obtained product was filtered through a 0.45µm membrane in order to remove impuritiescarried in during ultrasonication[12].

***Displacement or Injection method :***

 Solution of the lipid in a water-miscible solvent or a water- miscible solvent mixture (semi-polar water-miscible solvent, such as ethanol, acetone or methanol) is rapidly injected into an aqueous phase with or without surfactant. In this process, an o/w emulsion has been formed by injecting organic phase into the aqueous phase under magnetic stirring[9].

***Multiple Emulsion Technique :***

This is a modified solvent emulsification-evaporation method based on a w/o/w double emulsion. Drug (mainly hydrophilic drugs) was dissolved in aqueous solution, and then was emulsified in melted lipid. This primary was stabilized by stabilizer. It applied emulsification followed by solvent evaporation for the preparation of hydrophilic drug substance loaded SLN[9,10].



***Applications of NLCs***

***Oral drug delivery:***

Interest in NLCs for oral administration of drugs has been increasing in recent years. Increased bioavailability and prolonged plasma levels are described for peroral administration of NLCs. The lipid nanocarriers can protect the drugs from the harsh environment of the gastrointestinal tract. The lipophilic drugs can be entrapped by NLCs to resolve insolubility concerns. Repaglinide, an anti-diabetic agent with poor water solubility, has low oral bioavailability and a short halflife [13] . It is suitable to load into NLCs for improving oral delivery. [14] prepare repaglinide NLCs with Gelucire 50/13 as an amphiphilic lipid excipient. Gelucire 50/13(stearoyl macrogolglycerides) has been previously used for the preparation of solid dispersions for improving the aqueous solubility of lipophilic drugs [15]. DSC studies indicate that Gelucire 50/13 interacts with Precirol® and that this interaction suppresses polymorphic transitions of both components. The NLCs exhibit a significantly greater decrease of the blood glucose level (about 2-fold) in rats compared to marketed repaglinide tablets .

***Drug delivery to brain:***

Brain targeting not only increases the cerebrospinal fluid concentration of the drug but also reduces the frequency of dosing and side effects. The major advantages of this administration route are avoidance of first pass metabolism and rapid onset of action as compared to oral administration. LNC (e.g. NLC) of this generation are considered to be one of the major strategies for drug delivery without any modification to the drug molecule because of their rapid uptake by the brain, bioacceptability and biodegradability. Further, the feasibility in scale-up and absence of burst effect make them more promising carriers for drug delivery. In addition, NLC further enhanced the intranasal drug delivery of duloxetine in the brain for the treatment of major depressive disorder. Nanostructured Lipid Carriers (NLCs) of Asenapine maleate to improve the bioavailability and enhance the uptake of ASN to the brain [16].

***Pulmonary drug delivery:***

 Inhalation drug delivery represents a potential delivery route for the treatment of several pulmonary disorders. NLCs have greater stability against the shear forces generated during nebulization compared to polymeric nanoparticles, liposomes and emulsions.NLCs are comprised of an inner oil core surrounded by an outer solid shell and hence allow the high payload of a lipophilic drugs. NLCs in pulmonary disorders seems to be promising strategy since lung epithelium can be directly reached resulting in faster onset of action, desired dose and dosing frequency can be reduced as compared to other administered routes like oral and undesirable side effects of drugs can be avoided. Bioadhesive properties of NLCs are due to their small particle size as well lipophilic character lead to longerresidence time in lungs[17,18].

***Cancer Chemotherapy:***

In supplement, the function of NLC in cancer chemotherapy is presented and hotspots in research are emphasized. It is foreseen that, in the beside future, nanostructured lipid carriers will be further advanced to consign cytotoxic anticancer compounds in a more efficient, exact and protected manner. ZER into NLC did not compromise the anti-proliferative effect of ZER. Both ZER and ZER-NLC significantly induced apoptosis via the intrinsic pathway in time-dependent manner. The proposed mechanism of apoptosis of cancer cells induced by ZER and ZER-NLC is via activation of caspase-9 and caspase-3, inhibition of anti-apoptotic protein, and stimulation of proapoptotic protein expressions. Loading of ZER into NLC will increase the bioavailability of the insoluble ZER in the treatment of cancers[19] .g l-arginine lauril ester (AL) into nanostructure lipid carriers (NLCs) and then coating with bovine serum albumin(BSA),pH-sensitive membranolytic and lysosomolytic nanocarriers (BSAAL-NLCs) were developed to improve the anti-cancer effect y render more nanocarriers lysosomolytic capability with lower cytotoxicity, as well as improved therapeutic index of loaded active agents[20].

***Parasitic treatment:***

Novel colloidal delivery systems have gained considerable interest for antiparasitic agents with focus on 3 major parasitic diseases viz. malaria, leishmaniasis and trypanosomiasis. Lipid Nanoparticles combine advantages of traditional colloidal drug carrier systems like liposomes ,polymeric nanoparticles and emulsions but at the same time avoid or minimize the drawbacks associated with them. The delivery system should be designed in such a way that physicochemical properties and pharmacokinetic properties are modulated of the antiparasitic agents in order to improve biospecificity (targetablity) rather than bioavailability with minimization in the adverse effects associated with it. SLNs and NLCs have ability to deliver hydrophobic and hydrophilic drug with more physical and biocompatibility Dihydroartemisnin (Anti-malarial) loaded NLCs The drug release behaviour from the NLC exhibited a biphasic pattern with burst release at the initial stage and sustained release subsequently [21].

***Ocular delivery:***

The characteristic features of SLNs and NLCs for ocular application are the improved local tolerance and less astringent regulatory requirements due to the use of physiologically acceptable lipids. The other benefits include the ability to entrap lipophilic drugs, protection of labile compounds, and modulation of release behavior [22]. SLNs have been used for ocular drug delivery in the last decades. Recently, further investigations employing NLCs as ocular delivery systems have become knownIn Cyclosporine loaded NLCs the mucoadhesive properties of the thiolated nonionic surfactant Cysteine polyethylene glycol stearate (Cys PEG SA) and NLC modified by this thiolated agent were evaluated. Cys PEG SA and its resultant NLC provided a promising system with prolonged residence time [23] .

***Intranasal drug delivery:***

The use of nanocarriers provides suitable way for the nasal delivery of antigenic molecules .These represent the key factors in the optimal processing and presentation of the antigen. Nasal administration is the promising alternative noninvasive route of drug administration due to fast absorption and rapid onset of action, avoiding degradation of labile drugs (peptides and proteins) in the GI tract and insufficient transport across epithelial cell layers. The development of a stable nanostructured lipid carrier (NLC) system as a carrier for curcumin (CRM) biodistribution studies showed higher drug concentration in brain after intranasal administration of NLCs than PDS. The results of the study also suggest that CRM-NLC is a promising drug delivery system for brain cancer therapy [24) .In addition, NLC further enhanced the intranasal drug delivery of duloxetine in the brain for the treatment of major depressive disorder. Nanostructured Lipid Carriers (NLCs) of Asenapine maleate to improve the bioavailability and enhance the uptake of ASN to the brain[25].

***Parentral drug delivery:***

The nano-drug delivery systems such as nanomicelles, nanoemulsions and nanoparticles has displayed a great potential in improved parenteral delivery of the hydrophobic agents since last two decades. NLC has been considered as an alternative to liposomes and emulsions due to improved properties such as ease in manufacturing, high drug loading, increased flexibility in modulating drug release profile, and along with these, their aqueous nature and biocompatibility of the excipients has enabled intravenous delivery of the drug with passive targetingability and easy abolishment. Another reported example is NLCs of artemether (Nanoject) that offers significant improvement in the anti-malarial activity and duration of action as compared to the conventional injectable formulation. Nanoject can be considered as a viable alternative to the current injectable intramuscular(IM) formulation [26,27] .

***Cardiovascular treatment:***

Lipid nanoparticles as a carrier system has superiorities mainly prolonged circulation time and increased area under the curve (AUC) with manageable burst effect. NLCs would provide highly desirable physic-chemical characteristics as a delivery vehicle for lipophilic drugs. Drug loading and stability were improved. Tashinone (TA) loaded NLCs the in-vitro incubation tests confirmed that TA-NLC could bind to apoA-I specifically. Macrophage studies demonstrated that TA NLC incubated with native HDL could turn endogenous by association to apo-lipoproteins, which cannot trigger immunological responses and could escape from recognition by macrophages [28].Nifedipine loaded NLCs Nanoparticle suspensions were formulated with negatively charged phospholipid, dipalmitoyl phosphatidylglycerol in preventing coagulation to improve solubility and hence bioavailability of drug [29] .

***Cosmetic Applications of NLC:***

 Lipid nanoparticles—SLN and NLC—can be used to formulate active compounds in cosmetics, e.g. prolonged release of perfumes. Incorporation of cosmetic compounds and modulation of release is even more flexible when using NLC. In addition, the release of insect repellents has been described [30,31] . A feature of general interest is the stabilisation of chemically labile compounds. The solid matrix of the lipid nanoparticle protects them against chemical degradation, e.g. Retinol [32]and coenzyme Q10. A recently discovered feature is the sunscreen blocking effect of lipid nanoparticles. Similar to particles such as titanium dioxide the crystalline lipid particles scatter UV light, thus protecting against UV irradiation.

***CONCLUSION:***

In the20th century, Paul Ehrlich envisioned his magic bullet concept; the idea that drugs reach the right site in the body, at the right time, at right concentration. The aim has been to developed therapeutic nanotechnology undertaking, particularly for targeted drug therapy The smart NLCs as the new generation offer much more flexibility in drug loading, modulation of release and improved performance in producing final dosage forms such as creams, tablets, capsules and injectables. The effort to develop alternative routes and to treat other diseases with NLCs should be continued to extend their applications. Permeation via the gastrointestinal tract and BBB may be a future trend. The combination of two therapeutically active agents to be included in a single nanosystem is another consideration for future development.

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