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Recent Advances in Nanostructured Lipid Carriers for Biomedical Applications: A Review

Niveta Singh[1] and Seema Chawla[2]

[1,2]Department of Biomedical Engineering, D.C.R.U.S.T, Haryana, India
E-mail: [1]singhniveta@gmail.com

Abstract— *In the past few years, various nanotechnology platforms have been developed in the area of medical biology including both diagnostics and therapy (theranostics), and have gained phenomenal attention. Potential success relies on contemplating certain parameters such as nanoparticle fabrication methods, physical properties, drug loading efficiencies and most importantly, minimal toxicity of the carrier system itself.*

Nanostructured lipid carriers (NLCs) have captivated flourishing scientific and commercial surveillance in the last few years as alternate carriers for the pharmaceutical consignment. Nanostructured lipid carriers have been developed to deluge the shortcomings associated with solid lipid nanoparticles which were earlier proposed as an alternate carrier to emulsions, liposomes and polymeric nanoparticles. NLCs are lipid based nanoparticles which exhibit higher drug loading capability and are both biocompatible and biodegradable thus very well suited to medicinal application in targeted drug delivery and in vivo imaging. This paper provides an overview of NLC technology and describes different types of NLC, various formulation techniques, characterization and potential biomedical applications.

1. INTRODUCTION:

The development of nanoparticles has received considerable attention in the pharmaceutical sciences field due to the potential to modulate the pharmacological effect of nanoencapsulating active substances [1-3].Nanoparticles are colloidal particles ranging from 10 to 1000 nm (1.0 μm), in which the active principles (drug or biologically active material) are dissolved, entrapped, and/or to which the active principle is adsorbed or attached [6].Shortcomings often encountered with the colloidal schemes such as liposomes, nanocapsules, nanosponges and polymeric nanoparticles are the rapid degradation by the pH of the stomach or by the intestinal enzymes and the bile salts if taken orally, restricted physical and chemical steadiness throughout storage [8-10], need of large-scale output methods, a fast release of the drug from its carrier system, stability difficulties, the residues of the organic solvents used in the output method, the toxicity from the polymer [11,12] and numerous to say. All of these points make these colloidal carriers not optimal as a pharmaceutical carrier system.

Among the nanoparticles being explored at present, lipid nanoparticles preside as a result of their high degree of biocompatibility and versatility [4].

Lipid drug delivery systems offer advantages as to controlled release, stability, targetability, drug load, biodegradability, and ability of certain carriers to hold both lipophilic and hydrophilic drugs [4, 5].

Certain unique properties of lipid nanoparticles such as high surface to mass ratio, ability to absorb and carry other compounds such as drugs, probes and proteins forms the basis for their application to medical purposes. In general, lipid based nanoparticles are divided into 2 types: Solid lipid nanoparticles (SLNs) and Nanostructured lipid carriers (NLCs). Solid lipid nanoparticles were developed in the beginning of the 1990s as an alternative novel carrier system to liposomes, emulsions and polymeric nanoparticles. The matrix of SLN is made of pure solid lipid which is solid at room temperature and at body temperature). These solid lipids are arranged in highly ordered structure leaving very little space for encapsulation drug molecules, resulting in poor drug loading and storage stability. The end of 1990s saw the introduction of NLCs as improved versions of SLN wherein the solid lipid was partially replaced by liquid lipid.

2. CONCEPT OF NLC:

The basic objective behind development of NLC was providing the lipid matrix a stable nanostructure that could lead to increase in entrapment efficiency and prevent drug expulsion during storage (Muller et al., 2000b) [13].NLCs are nanosized drug delivery systems formulated using a blend of spatially different lipids (a mixture of solid and liquid lipid) (Carbone et al. 2014)

NLC have been developed to deluge the shortcomings associated with solid lipid nanoparticles which were earlier proposed as an alternate carrier to emulsions, liposomes and polymeric nanoparticles. NLC exhibit higher drug loading capability as compared to SLN by blending a fluid lipid with the solid lipid. Advantages of NLC can be enumerated as follows:

- Better physical stability
- Ease of preparation and scale-up,
- Increased dispersability in an aqueous medium,
- High entrapment of lipophilic drugs and hydrophilic drugs,
- Controlled particle size,
- An advanced and efficient carrier system in particular for lipophilic substances,
- Increase of skin occlusion,
- Extended release of the drug,
- Improve benefit/risk ratio,
- Increase of skin hydration and elasticity [17-19]

3. TYPES OF NLCS

Different types of NLCs can be obtained on the basis of way of production and the composition of the lipid blend. The basic idea is that by giving the lipid matrix a certain nanostructure, the pay-load for active compounds is increased and expulsion of the compound during storage is avoided. The three types can be summarized as follows:

1) The imperfect type
2) The amorphous type
3) The multiple type

The imperfect type of NLC has the least amount of liquid-phase lipid (oil) and is composed of saturated and unsaturated lipids with varying fatty acid chain lengths, which lead to defects in the lipid matrix and compartments for drug storage. The imperfect NLC is prone to an expulsion of drugs during the crystallization process of production [7].

The multiple type of NLC avoids this drug expulsion by incorporating a higher concentration of liquid-phase lipids in the lipid matrix. During the cooling process, oil reaches its solubility limit and precipitates into nanocompartments [7].The amorphous type of NLC forms solid lipid that lacks any crystalline structure. This is achieved through the use of lipids such as hydroxyoctacosanyl hydroxystearate isopropyl-myristate [7].

4. PRODUCTION TECHNIQUES OF NLC

There are various formulation approaches that exist for the production of nanolipid carriers. These approaches have been adopted from polymeric nanoparticle production procedure. The various methods applied in the preparation of NLC are high pressure homogenization [21, 22], microemulsion [23, 24], phase inversion [25, 26], emulsification sonification [27], solvent emulsification-evaporation [28], solvent diffusion, solvent injection/ solvent displacement method [29], membrane contractor etc. [30]. NLC may be produced by various traditional techniques, the preferred production method being high pressure homogenization through which large scale production is possible. The two recent methods for the production of NLC are phase inversion and membrane contractor.

4.1 HPH (High Pressure Homogenization)

HPH has been used as a reliable and powerful technique for the large-scale production of NLCs. The lipid is pushed with high pressure (100 – 2000 bars) through a very high shear stress, resulting in disruption of particles down to the submicrometer or nanometer 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. Homogenization may be performed either at elevated temperature (hot homogenization) or below room temperature (cold homogenisation) [32].

4.2 Hot Homogenization Technique

In this technique the drug along with melted lipid is dispersed under 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 [33].

4.3 Cold Homogenization Technique

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 [34].

4.4 Microemulsion Technique

In this technique, the lipids are melted and drug is incorporated in molten lipid. A mixture of water, co-surfactant(s) and the surfactant is heated to the same temperature as the lipids and added under mild stirring to the lipid melt. A transparent, thermodynamically stable system is formed when the compounds are mixed in the correct ratios for microemulsion formation. This microemulsion is then dispersed in a cold aqueous medium under mild mechanical mixing of hot microemulsion with water in a ratio in the range 1:25 – 1:50. This dispersion in cold aqueous medium leads to rapid recrystallisation of the oil droplets [35]. Surfactants and co-surfactants include lecithin; biliar salts along with alcohols such as butanol. The microemulsion is prepared in a large, temperature-controlled tank and then pumped from this tank

into a cold water tank for the precipitation step [36]. Figure1 shows formation of NLC nanosuspension [10].

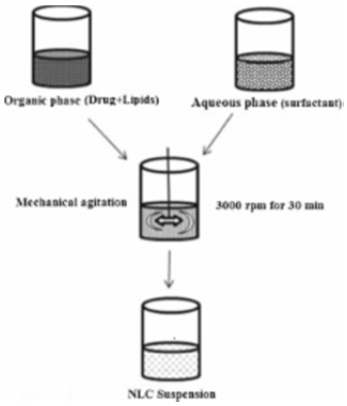

Fig. 1: Formation of NLC suspension

5. CHARACTERIZATION OF NLCS

Intensive characterisation of the structure and mixing behaviour of NLCs is essential for studying their behavior.

5.1 Particle size and zeta potential

Photon Correlation Spectroscopy (PCS) is an established technique used for measurement of size and distribution Polydispersity Index (PI) of NLC [13].

5.2 Entrapment efficiency (%) and Drug Loading

Drug entrapment efficiency (EE) and drug loading (L) of nanoparticles can be calculated after separation of the free drug from aqueous NLC dispersion, using centrifugation or ultrafiltration (Hu et al., 2006).

5.3 Polydispersity Index (PDI)

Due to poly disperse nature of Nanostructured lipid carriers, measurement of poly dispersity index (PI) is important to know the size distribution of the nanoparticles. The lower the PI value, the more mono dispersed the nanoparticle dispersion is.

5.4 Shape and Morphology

Scanning electron microscopy (SEM)and transmission electron microscopy (TEM) are very useful techniques to determine the shape and morphology of NLCs. These techniques can also determine the particle size and size distribution. SEM utilizes electron transmission from the sample surface, whereas TEM utilizes electron transmission through the sample. Although normal SEM is not very sensitive to the nanometer size range, field emission SEM (FESEM) can detect nanometer size range [41]. Spherical shape of the Nanostructured lipid nanoparticles is reported.

6. APPLICATIONS OF NLCS

Nanostructured lipid carriers as nano carriers can find applications in various fields. The various applications can be broadly categorized into therapeutic applications which mainly focuses on the various routes of administration in drug delivery and second category focuses on fields like cosmetics, nutraceuticals and gene delivery [20].

6.1 Therapeutic Applications

6.1.1 NLCs for topical drug delivery

An invention by the Indian company V. B. Medicare describes a method to prepare an NLC-based nanogel formulation [37], aimed at increasing the local bioavailability of drugs on the skin and/or enhance their dermal delivery. An example is reported using the anticancer agent 5-fluorouracil, which showed an improved permeation in vitro (Franz cell assay) and after application on the skin [37].

6.1.2 NLCs for Brain Targeting

In this field of application, one of the first inventions relates to the treatment of Alzheimer's disease and other age-related disorders using a curcuminoid-loaded composition [37]. A recent NLC formulation consisting of glyceryl disterate and glyceryl behenate as solid lipid and glyceryl triacetate as liquid lipid at room temperature has been recently patented for the delivery of antioxidants (coenzyme Q10), for the treatment of neurodegenerative disorders such as Alzheimer's disease and Parkinson's disease [37]. The NLC are gaining interest as carriers across the Blood-Brain Barrier (BBB).

6.1.3 NLCs for Oral Delivery

NLCs have been proved as one of the beneficial systems for peroral administration of poorly water soluble drugs having low bioavailability. Another important feature is the high dispersity of NLCs due to which they exhibit a high specific surface area for enzymatic attack by intestinal lipases. Other advantages include increased drug loading; improved drug inclusion; patient compliance; high particle concentration and cream like consistency of the carrier [20].The mechanisms involved in the absorption of the NLC from the intestine include direct uptake through the GI tract, increase in permeability by surfactants and decreased degradation and clearance. Besides this, the NLCs can also adhere on to the gut wall prolonging the residence time, and consequently the absorption [20].

6.1.4 NLCs for Ocular Drug Delivery

Recent reports indicated that NLC could increase the ocular bioavailability of lipophilic drug, ibuprofen. Our previous research showed that NLC could improve the penetration of bioactive compounds into ocular tissues with a good ocular tolerance.

6.1.5 Diagnostics and Imaging

An interesting invention for applications of NLC in imaging, provides the formulation of novel lipid nanoparticles with metal or nonmetal core for multimodality imaging. An application regarding the use of synthetic NPs for the delivery of imaging agents used in MRI, computerized tomography scanning, gamma scintigraphy or optical imaging techniques for diagnostic applications [44].

6.2 Other Applications

6.2.1 Cosmetics

Recently NLCs have been developed based on the controlled nanostructuring of particle matrix which provides immense advantages with respect to loading capacity and long term stability. The various forms in which NLC dispersions can be given are gel, cream, lotion, ointment. The beneficial aspects associated with these NLCs in cosmaceuticals 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 [42].

6.2.2 Nutraceuticals

Nutraceuticals are bioactive compounds, which provide medicinal or health benefits. Carotene-NLC with highly antioxidant and significant anti-bacterial activities were successfully produced by using natural oils and a versatile high-shear homogenisation technique. Hesperetin (5,7,3 ′ -trihydroxy-4 ′ -methoxyflavanone) belonging to flavonones, which is useful in chemically induced mammary tumorigenesis, colon carcinogenesis, heart attack and blood pressure was also successfully encapsulated in NLCs that showed good acceptance, homogeneity, improved taste and enhanced therapeutic effects [43].

7. LIMITATIONS OF LIPID NANOPARTICLES

Despite the great potential of NLCs in targeted delivery, they face certain limitations like: Cytotoxic effects related to the nature of matrix and concentration, irritative and sensitizing action of some surfactants and lack of sufficient preclinical and clinical studies with these nanoparticles in case of bone repair [20].

8. CONCLUSION

The current review focuses on various applications of nanostructured lipid carriers in different bio medical and diagnostic areas. Nanoparticle lipid carriers (NLCs) provide a potential perspective for improving the bioavailability of highly lipophilic drugs with poor aqueous solubility so that they can be exploited for biomedical applications. Distorted matrices of NLC ultimately lead to higher drug loading, higher drug entrapment, modulated drug release and thus enhanced drug absorption.

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