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Nanostructured Lipid Carriers: An Excellent Tool for Drug Delivery

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ABSTRACT
Nanocarriers present a great approach in drug delivery. Nanostructured lipid carriers (NLCs) are a recent approach for the delivery of poorly soluble drugs with low oral bioavailability. Nanostructured Lipid Carriers (NLCs) are mixture of solid lipids along with spatially incompatible liquid lipids. It remains solid at room temperature. It also overcomes the disadvantages of various lipid particulate carriers. The present review gives insights on the definitions and characterization of NLC as colloidal carriers including the production techniques.
KEYWORDS: Nanotechnology, targeted drug delivery, nanocarrier, NLCs.

I. INTRODUCTION

In recent years, it has become evident that the development of novel drugs is insufficient for guaranteeing progress in drug therapy. Exciting experimental data obtained *in-vitro* is often followed by disappointing results in the *in-vivo* or clinical situation. Predominant reason for this failure are the insufficient drug concentration in the body, high drug toxicity because of extensive distribution, poor drug solubility in formulation and high drug fluctuation or inter subject variability of plasma drug level [1]. A promising approach to overcoming this problem is the development of feasible drug delivery system. During the past decades, some strategies have been developed such as nano-sized drug carrier system [2], which is a great approach in drug delivery with the promising features of protection of drug from degradation and cleavage, controlled release and the delivery of drug molecules to the target sites [3]. Drug carrier materials play a significant role in delivery of drug. These carriers can be processed into different release system such as microspheres, microcapsules and nanoparticle [4]. Lipid nanoparticles made with a solid matrix is derived with the help of pharmaceutical nanotechnology which gains a huge impact on the pharmaceutical field. Generally a solid lipid nanoparticle is composed of physiological lipids disposed in an aqueous surfactant solution. It has certain benefits like improvement in solubility, bioavailability and also improvement in drug therapy [5]. There are some drawbacks such as loading insufficiency due to formation of perfect crystalline structure, drug expulsion and also high water content in the preparation [6,7]. In order to overcome these drawbacks a new drug carrier system is developed known as nanostructured lipid carriers (NLCs). NLCs are a blend of a solid and the liquid lipids that form an imperfection in lipid matrix in which high amount of drug can accommodate. Problems like drug expulsion, loading insufficiency also reduced with the introduction of the NLCs. NLCs are the asset in the terms of targeted drug delivery of the drug to the respective organ of the body such as brain targeting and tumor targeting [8,9].

II. NANOSTRUCTURED LIPID CARRIERS

Nanostructured lipid carriers (NLCs) are a type of submicron particulate drug delivery system based on mixture of solid lipids with spatially incompatible liquid lipids [10]. The usual particle diameters of the NLCs are in the range of approximately 10–1000 nm. It remains solid at room temperature. It has various advantages like controlled release of drug from the carrier, biocompatible lipids, feasible to produce on large scale using the existing machinery, avoid first pass metabolism and drug protection from biochemical degradation [11].

III. DIFFERENT TYPES OF NLCS

There are three types of NLCs such as

(i) TYPE 1: Amorphous structured NLCs (Non crystalline NLCs)

These type of NLCs are developed by preventing the crystallization of the mixing solid and the liquid lipids due to which there is a formation of a amorphous structured lipid matrix which create high amount of space within the lipid matrix in which high amount of drug can be incorporated and reduce the problem associated with SLN preparation as shown in the **Figure 1** [12].

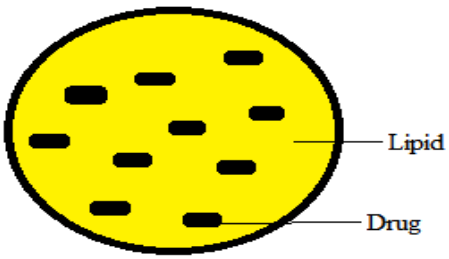

Figure 1: Type 1

(ii) TYPE 2: Imperfect structured NLCs

In this solid lipids and liquid lipids (oils) are blended. During the production process, the liquid lipid particles (nanoemulsions) are cooled from the molten state to room temperature to crystallize and form solid particles. At high oil concentrations a miscibility gap of the two lipids occurs during the cooling phase which leads to phase separation that means precipitation of tiny oily nanocompartments as shown in the **Figure 2** [13].

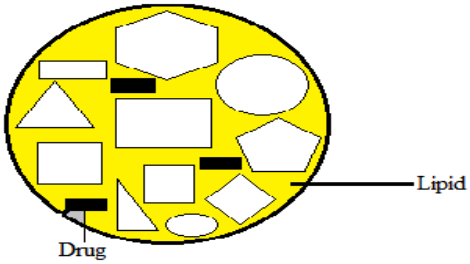

Figure 2: Type 2

(iii) TYPE 3:Multiple structured NLCs

These types of NLCs are made up of oil, fat, water and stabilizer. Large amount of liquid lipids are used in multiple structured NLCs as compared to other lipids structured formulations. Large amount of liquid lipids are blended with the solid lipids due to which there is a formation of small liquid lipids packets supported by the solid lipid matrix and desired amount of drug can be introduced into the formulation as shown in the **Figure 3** [14,15].

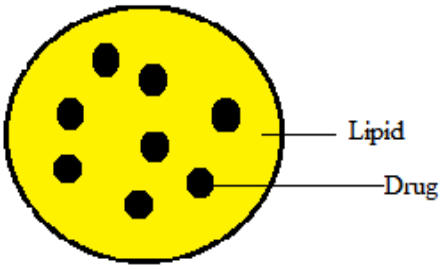

Figure 3: Type 3

IV. ADVANTAGES OF NLCS

1) NLCs are easy to scale up and inexpensive as compared to polymeric/surfactant based carrier [16].
2) NLCs transport both lipophilic and hydrophilic drug at the same time [17].
3) NLCs are easier to validate and get easy approval from regulatory bodies [18,19].
4) NLCs have excellent bioavailability [20,21].
5) Most lipids used in NLCs are biodegradable [22].
6) NLCs have improved skin penetration due to small particle size.

V. STRUCTURAL COMPONENTS OF NLCS

(i) Lipids

A lipid is chemically defined as a substance that is insoluble in water and soluble in ether and chloroform. Lipids are an important component of livings cells.

I. Solid lipids

Solid lipids are the combinations of numerous chemical compounds having a melting point more than 40° C. These solid lipids are well tolerated, accepted for human use and also biodegradable in nature [23,24]. Following are some examples of solid lipids

1) Triglyceride (Tristearin, Trilaurin)
2) Monoglyceride (Glycerol monosterate)
3) Fatty acids (Stearic acid, Palmitic acid)
4) Waxes (Cetyl palmitate, Beeswax)

II. Liquid lipids

The liquid lipids used are digestible oils obtained from natural sources [25]. Natural and synthetic oils are used such as castor oil, mustard oil, cod-liver oil, medium chain triglycerides and oleic acid.

(ii) Emulsifier

They are used to stabilize the liquid nanoparticle dispersion and also prevent particle agglomeration in the dispersion. Choice of ideal emulsifying agent depends on certain properties like charge, molecular weight and HLB balance [26,27]. Emulsifying agent decreases the interfacial free energy or interfacial tension between two phases [28] which forms a stabilized preparation. Following are some examples of emulsifier

1) Polysorbitan esters (Polysorbate 20, Polysorbate 40)
2) Polyoxyl castor oil derivatives (Polyoxyl 35, Polyoxyl 40)
3) Sorbitan esters (Sorbitan monosterate, Sorbitan monopalmitae)

VI. METHOD OF PREPARATION

(i) Solvent based method

In this method lipid nanoparticle are prepared with the help of different type of organic solvents such as cyclohexane, isopropanol, methyl chloride. Solvent based method is developed to overcome the problems occurs during the hot homogenization method such as loss of active constituents and decrease in capability of emulsifying agent which reduce the stability of the preparations. Further solvent based method is categorized into two categories

I. Solvent injection or displacement method

Method in which a solvent that distributes very rapidly in water (ethanol) is used [29]. Firstly the drug is incorporated into the lipid matrix which is then added into the organic solvent such as ethanol and then organic phase is injected into the aqueous solution of emulsifying agent with the help of injection. After sometime when lipid and drug dispersion comes in contact with the emulsifying agent in the water lipids starts precipitating and encapsulate the drug and form the desired amount of nanoparticle which can be filtered out from the solution [30,31].

II. Solvent emulsification evaporation method

It consists of two different phases; organic phase and aqueous phase. Firstly the hydrophobic drug is mixed into the solution of lipids and the water miscible organic solvent. In next step the organic phase is added into the aqueous phase containing the desired amount of emulsifying agent and then homogenized by using high shearing device. At last, the lipid nanoparticles can be obtained by evaporating the organic solvent by using the mechanical stirrer under reduced pressure [32,33].

(ii) High pressure homogenization technique

High-pressure homogenization technique is one of the common and the powerful technique for the production of lipid nanoparticles, which has certain advantages over other techniques. NLCs production can be done with the help of two methods such as [34].

I. Hot homogenization technique

Hot homogenization is carried out at temperatures above the melting point of the lipid (100° C above the melting point of the lipid) and can therefore be regarded as the homogenization of an emulsion. At initial stages active constituent is mixed in the lipid matrix which is completely melted. In next step dispersion of the drug and lipids are pre-emulsified by the addition of an emulsifier followed by using high shearing device which stabilizes the hot solution. Further in continuation the emulsified hot solution is passed through high pressure homogenizer which forms the nano-emulsion which is at last cooled down and re-crystallise at room temperature forms the nanoparticle collected by centrifugation method [35,36]

II. Cold homogenization technique

Cold homogenization technique is suitable for heat-labile drugs or hydrophilic drugs. The lipid and drug are melted together and rapidly cooled under liquid nitrogen forming solid lipid micro particles; a pre-suspension is formed by homogenization of the particles in a cold surfactant solution. The pre-suspension is then further homogenized in a high pressure homogenization at or below room temperature at predetermined homogenization condition to produce NLCs. In this both high pressure homogenization techniques are suitable for processing lipid concentrations of up to 40% and generally they yield very narrow particle size distributions. Cold homogenization minimizes the thermal exposure of the sample [37].

(iii) Micro emulsion technique

The lipids (fatty acids or glycosides eg. lipid acid) are liquefied and in this liquefied lipid the drug is dissolved. A mixture of water, surfactant and co-surfactant is heated at the same temperature as the lipid and added to the lipid melt under mild stirring. A clean micro emulsion was obtained when the components were mixed in correct ratio. The formed micro emulsion is the basis for the nanoparticle formation of a requisite size. This micro emulsion is then dispersed in a cold aqueous medium under mild mechanical mixing of hot micro emulsion with water during a quantitative relation in the range 1:25-1:50. This dispersion in cold aqueous medium leads to rapid recrystalization of the oil droplets [38]. The micro emulsion was prepared in a large temperature-controlled tank and then pumped from this tank into a cold water tank for precipitation purpose [39].

(iv) 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 [40].

VII. CHARACTERIZATIONS OF NLCS

(i) Particle size analysis

Particle size is one of the most important characters of nanoparticle which help in the determination of the quality of the preparation. Dynamic Light Scattering is one of the method help in determination of particle size of the lipid particle with the measurement of fluctuation in light intensity due to the particle movements in the solution [41].

(ii) Zeta potential

It is also known as Electro Kinetic Potential which is defined as the difference between the shears plane and the electro neutral region of the solution. It is measured to evaluate the particle size and the stability of the lipid nanoparticle preparation by assessing the aggregation and the dispersion processes [42].

(iii) Differential Scanning Calorimeter

It is the number of physical and chemical changes to the solid nanoparticle within a sample due to the influence of gain or loss of heat. These physical and chemical changes such as degree of crystalline and melting behavior can be evaluated by using the technique known as DSC [43]. The degree of crystalline of NLCs is calculated from the ratio of NLCs enthalpy to the bulk enthalpy. Bulk enthalpy calculated on the basis of total weight taken of the preparation [44].

(iv) Scanning Electron Microscopy

It is a type of electron microscopy which produces the images of sample by scanning the surface of the particles with the help of beam of electrons. It helps in observing the shape and morphology of the particles [45].

(v) Drug Encapsulation Efficiency

Encapsulation efficiency is one of the important parameter for NLCs that provide information towards the releasing characteristics of the active constituents encapsulated in the lipid matrix. It is defined as percentage of drug that is successfully entrapped into the nanoparticle [46].

(vi) Drug release studies

Nanostructured lipid carriers are the engineered encapsulated active constituent in the lipid matrix that exhibits the controlled or sustained release of the active constituent into lipid core over an extended period after the administration of the single medicament to achieve the prolonged therapeutic effect. Most common methods utilize to study the *in vitro* release of the active constituents from the NLCs are the dialysis and the Franz diffusion cell with the sink conditions. There are many factors that could affect the release profile of the drug from the nanoparticle are particle size, lipid matrix and different type of surfactants [47,48].

(vii) Nuclear Magnetic Resonance

NMR spectroscopy is used to investigate the mobility of material in the inner core of the NLCs. The mobility of the material depends on the width at half amplitude of the signals [49]. Broad signals and small amplitudes are characteristics of the molecules with restricted mobility and strong interactions [50].

VIII. APPLICATIONS OF NLCS

There are various applications of NLCs (As shown in **Figure 4**) in the pharmaceutical field some are as follows:

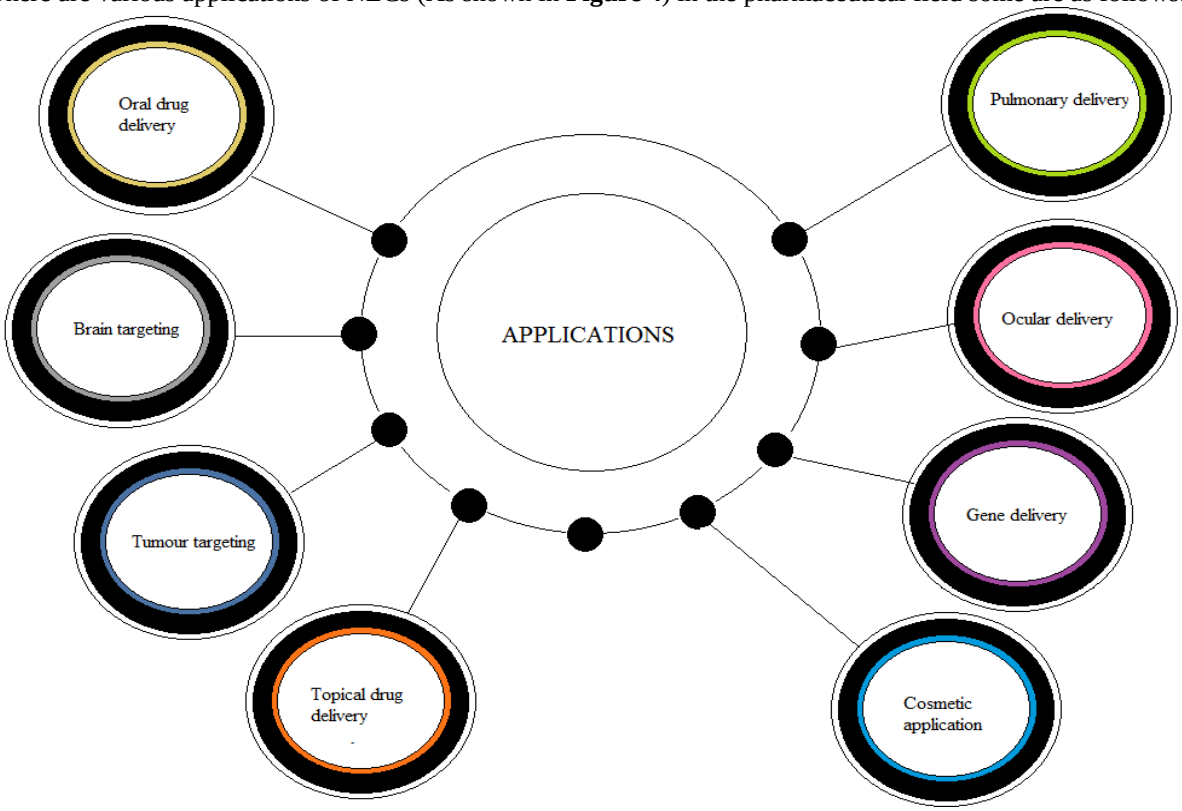

Figure 4: Application of NLCs

(i) Oral drug delivery

NLCs have been proved one of the beneficial systems for the oral administration of poor water-soluble drug having low bioavailability. Lipid nanocarrier protects the drug from the enzymatic attack and also the harsh environment of GIT tract. Another advantage of introduction of NLCs by oral cavity is improved patient compliance and increased drug loading capacity. Repaglinide loaded nanostructured lipid carriers with size range of 50-100nm were designed to enhance absorption of poor water soluble drug as compared to large particle size such as 325nm and also improves oral bioavailability [51]. Lovastatin loaded nanostructured lipid carrier has improved bioavailability given by oral drug delivery system [52].

(ii) Brain targeting

Targeting of drug to the brain by using the NLCs increases the cerebra spinal fluid concentration and reduces the frequency of dosing and side effects. NLCs of Apomorphine has improved duration of brain targeting and accumulation in brain by intravenous delivery [53,54].

(iii) Tumor targeting

Formation of anticancer drug loaded in nanostructured lipid carriers can overcome the limitations like low water solubility, high systemic toxicity and insignificant cellular uptake. For example Paclitaxel loaded in the lipid carrier were modified with folic acid and polyethylene glycol prepared by solvent evaporation method using cholesterol, tocopherol, lecithin and poloxamer have an effective anticancer agent [55].

(iv) Topical drug delivery

Drug penetration through the skin is always limited due to impermeability of the skin and other concerns are delivery of the drug to the action site in a sufficient manner, to overcome some problems NLCs are developed [56]. Bioavailability of drug through skin can be improved using nanocarrier because of small particulate size ensuring close contact to subcutaneous tissue [57]. Aceclofenac gel loaded in the nanostructured lipid carriers prolong its action and enhance permeation to skin due to small particle size [58]. Acitretin loaded in nanostructure lipid carriers used for psoriasis treatment with a promising efficacy [59,60].

(v) Pulmonary delivery

NLCs due to their small size and their lipophilic character leads to the longer retention time and good adhesion in the lungs, which improved and prolonged the therapeutic character and better compliance for patient [61]. Celecoxib loaded nanostructured lipid carriers used in the lung cancer [62]. Itraconazole loaded nanostructured lipid carriers has a pulmonary application [63].

(vi) Ocular delivery

Ocular drug delivery has been a major challenge to pharmacologist and drug delivery scientist to deal with static barrier and dynamic barrier, but these barriers can be overcome by using NLCs [64]. Olfoxacin loaded NLCs base inserts for ocular application treatment of bacterial keratitis [65]. Flubiprofen loaded NLCs based on stearic acid used as anti-inflammatory ocular therapy [66].

(vii) Gene delivery

Gene loaded in NLCs can be used as anon-viral gene transfer vector that offers a promising approach for gene therapy [67]. Use of small interfering RNA can be used as silencing oncogenic target such as surviving, which has great potential for treatment of cancer, but there is a limitation, which is their short action [68], this problem can be overcome by using NLCs [69].

(viii) Cosmetic application

Nanostructured lipid carriers are one of the excellent vehicles for cosmetic application due to their excellent characteristics against chemical degradation and enhancement of water content of skin [70,71]. Lutein loaded nanostructure lipid carriers are developed to evaluate the stability and skin targeting. NLCs with organic filters are developed with an increased sun protection factor compared to nanoemulsions [72].

IX. CONCLUSION

Nanostructured lipid carriers are the new generation of nanoparticle active substance vehicles and are attracting major attention as novel drug carrier system. NLCs hold great promises for reaching the goal of controlled and site specific drug delivery. They are also suitable for use in the food industry especially for the poor water soluble active compounds. Type and concentration of lipids and emulsifier have a significant effect on loading capacity, entrapment efficiency and physicochemical stability. However in future it is expected that utility of NLCs in basic research and clinical setting will be more extensive and leads to discover of new therapies for the treatment of various diseases.

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