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Nanostructured lipid carriers for site-specific drug delivery

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ABSTRACT

Nanostructured lipid carriers (NLC), comprises of a blend of solid and liquid lipids which results in a partially crystallized lipid system and imparts many advantages over solid lipid nanoparticles such as enhanced drug loading capacity, drug release modulation flexibility and improved stability. NLC have found numerous applications in both pharmaceutical and cosmetic industry due to ease of preparation, the feasibility of scale-up, biocompatibility, non-toxicity, enhanced targeting efficiency and the possibility of site-specific delivery via various routes of administration. This review highlights the NLC with focus on the structure, the various fabrication techniques used and the characterization techniques which are critical in the development of a suitable and stable formulation. The review also provides an insight into the potential of NLC as site-specific delivery systems and the therapeutic applications explored via various routes of administration.

1. Introduction

Nanoparticulate carriers, with their nanoscale dimensions and distinct properties, have shown great promise as delivery systems in the recent years. Their advantages include protection of the active ingredient by providing protection against moisture, physiological pH and enzymes, enhanced bioavailability, dose reduction, controlled drug release, prolonged circulation time, improved intracellular penetration and targeted delivery to specific sites or organs by surface modifications of the carriers. They also act as carriers for a variety of molecules including peptides and proteins, contrast agents, antibodies, RNA, etc. [1,2]. A variety of nanocarriers such as nanocrystals [3,4], nanotubes and nanowires [5–7], liposomes [8,9], polymeric nanoparticles [10,11], hydrogels [12,13], dendrimers [14] and lipid nanoparticles [15,16] have been designed for drug delivery and diagnostic purposes [17].

Lipidic drug delivery systems have gained attention in the past few decades primarily due to their biocompatibility as compared to polymeric and inorganic nanoparticulate delivery systems, in addition to their capability of permeating challenging physiological barriers, especially the blood-brain barrier (BBB) due to their lipophilicity, even without surface modifications. Further, ease of preparation, cost-effectiveness and the feasibility of large-scale production is making these delivery systems more attractive [18,19].

2. Types of lipid carriers

Lipid carriers can be categorized into various types depending on their method of preparation and physicochemical characteristics. They include liposomes, niosomes, solid lipid nanoparticles (SLN) and nanostructured lipid carriers (NLC).

Liposomes are spherical vesicles consisting of one or more phospholipid bilayers fabricated from cholesterol and other natural phospholipids enclosing an aqueous core [20,21]. At present, a number of liposome formulations have received approval for various conditions including doxorubicin for various cancers (Doxil®, Myocet® and Lipodox®), amphotericin B for severe fungal infections (Ambisome®), cytarabine for lymphomatous meningitis (Depocyt®), morphine sulfate for management of pain (DepoDur®), inactivated hepatitis A virus (strain RG-SB) for hepatitis A (Epaxal®) and inactivated hemagglutinin of Influenza virus strains A and B for influenza (Inflexal®) among many others [22]. The applications of liposomes are limited attributable to issues such as short shelf life, poor stability, low encapsulation efficiency especially for hydrophilic drugs and rapid uptake followed by elimination by the reticuloendothelial system (RES) [19].

Niosomes are vesicles composed of non-ionic surfactants and cholesterol or its derivatives. Like liposomes, they have the ability to load both hydrophilic and lipophilic molecules besides being more economical and physically stable than liposomes [23,24].

SLN are composed of solid lipids stabilized in an aqueous dispersion with the help of emulsifying agents [18,25]. SLN can effectively deliver a variety of molecules including both lipophilic and hydrophilic drugs,

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oligonucleotides, genes, peptides and vaccines. Further, they have the advantage of biocompatibility, fast and effective production, scalibility in manufacturing and in many cases avoiding the use of organic solvents during production. Their limitations include low drug loading capacity due to the crystalline nature of the lipids, expulsion of the encapsulated drug due to the formation of a perfect crystalline lattice (β-modification) of the lipid and gelation in the dispersed phase during storage [26–28].

NLC are a new generation of solid lipid nanoparticles which were developed to overcome the limitations of SLN. NLC also exists as a solid matrix of lipids at room and body temperature. However, instead of using only a solid lipid, a portion is replaced by an oil resulting in a less ordered lipid matrix providing enhanced drug loading and preventing leaching out of the drug during storage [28,29].

In the next sections of this review, we will discuss the types, fabrication methods, characterization techniques, applications and future of NLC as drug delivery systems.

3. Types of NLC

Based on the variation in the composition of lipid and oil mixtures in addition to the various fabrication methods, NLC can be categorized into three types:

a The imperfect type
b The amorphous type
c Multiple oil-in-solid fat-in-water (O/F/W) type

Imperfect type NLC involves mixing of spatially different lipids such as glycerides, composed of a number of fatty acids, which introduce imperfections in the crystal order. The drug loading can be further increased by increasing imperfections by using a mixture of various glycerides, varying in saturation and length of carbon chains.

In the amorphous type, a structureless amorphous matrix is formed by mixing special lipids such as hydroxyoctacosanyl hydroxystearate or iso-propyl myristate with the solid lipid. As a result the NLC exists in an amorphous state rather than an ordered state which prevents the drug expulsion resulting from β-modification during storage.

Multiple O/F/W type NLC contains numerous nanosized liquid oil compartments distributed in the solid matrix. Drug solubility is higher in these nanosized compartments which results in increased drug loading. Further, the release is prolonged because the compartments are surrounded by a solid lipid matrix [30–32]. Fig. 1 illustrates the various types of NLC in comparison to SLN.

4. Methods of fabrication

4.1. Formulation ingredients

Like lipid nanoemulsions which are majorly oil in water (O/W) type, the major components of NLC are lipids, surfactants and water. However, a proportion of oil is replaced by a solid lipid resulting in a solid lipid matrix at room temperature. The solid lipids are blended with oils preferably in the ratio ranging from 70:30 to 99.9:0.1. In multiple emulsion NLC, a higher proportion of oils can be used. The system is stabilized with the help of 0.5% to 5% surfactant solutions. Various lipids, oils and surfactants commonly used in the formulation of NLC are enlisted in Table 1.

4.2. Fabrication techniques

A number of techniques have been successfully used for the production of NLC. These techniques are high pressure homogenization (HPH) [33–37], microemulsion [38–40], emulsification-solvent evaporation method [41,42], emulsification-solvent diffusion method [43,44], solvent injection (or solvent displacement) method [45], phase inversion [46], multiple emulsion [47], ultrasonication [48] and membrane contractor technique [49]. The various methods are summarized in Table 2. However, the preferred method is HPH due to the fact that it is already used in the pharmaceutical industry for preparation of emulsions for nutrition [50] and hence a feasible method for large-scale production.

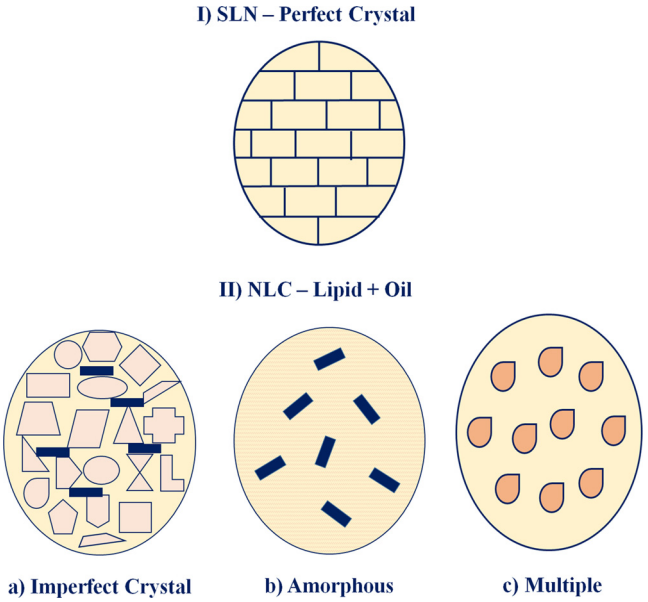

Fig. 1. Types of NLCs (II) in comparison with the ordered SLN (I). The NLC types are: a) imperfect crystal, b) amorphous and c) multiple type.

Table 1
Formulation ingredients for NLC.

Formulation Ingredients	Examples	Reference
Solid lipids	Stearic acid	[38,78]
	Glyceryl Monostearate (GMS)	[35,43,85,136,137]
	Carnauba wax	[138]
	Cetyl palmitate	[154,68,161]
	Glyceryl Palmitostearate (Precirol® ATO 5)	[46,58,139,155,157]
	Glyceryl Behenate (Compritol® 888 ATO)	[35,37,140]
	Grades of Witepsol® [37,74,141]	[37,74,141]
	Grades of Softisan® [45]	[45]
	Gelucire® [40]	[179,183]
Liquid lipids	Soybean oil	[113]
	Medium chain triglycerides (MCT)/caprylic and capric triglycerides	[35,37,43,85,140,141]
	Oleic Acid (OA)	[38,74]
	Isopropyl Myristate	[142]
	α-tocopherol/ Vitamin E	[46]
	Corn oil	[113]
	Squalene	[58,139]
Surfactants	Poloxamer 188	[35,37,85]
	Tween® 80	[37,74,140]
	Tween® 20	[44]
	Myverol™ 18-04 K	[58,139]
	Sodium dodecyl sulfate (SDS)	[78]
	Sodium deoxy cholate (SDC)	[37,85]
	Polyvinyl alcohol (PVA)	[43,141]
	Lecithin	[35,85]
	Solutol® HS 15	[35]
	Polyoxyl castor oil	[44,105]