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Review Article

Solid Lipid Nanoparticles and Nanostructured Lipid Carriers: Structure, Preparation and Application

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Abstract

Lipid nanoparticles (LNPs) have attracted special interest during last few decades. Solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs) are two major types of Lipid-based nanoparticles. SLNs were developed to overcome the limitations of other colloidal carriers, such as emulsions, liposomes and polymeric nanoparticles because they have advantages like good release profile and targeted drug delivery with excellent physical stability. In the next generation of the lipid nanoparticle, NLCs are modified SLNs which improve the stability and capacity loading. Three structural models of NLCs have been proposed. These LNPs have potential applications in drug delivery field, research, cosmetics, clinical medicine, etc. This article focuses on features, structure and innovation of LNPs and presents a wide discussion about preparation methods, advantages, disadvantages and applications of LNPs by focusing on SLNs and NLCs.

Introduction

liposomes are traditional models of lipid-based formulations which were invented in 1965 and have been widely studied in recent decades.[1] A liposome is defined as a spherical vesicle with an aqueous internal cavity enclosed by a lipid bilayer membrane. The name of liposome is resulting from two Greek words, 'lipid' meaning fat and 'soma' meaning body. They have been investigated in recent decades for dermal, pharmaceutical and cosmetics studies. Liposomes have unique advantages as a pharmaceutical carrier such as protection of drug against enzymes degradation, low toxicity, flexibility, biocompatibility, entirely biodegradablity and non-immunogenicity.[2-4] However, many of its applications are limited due to some disadvantages such as short shelf life, poor stability, low encapsulation efficacy, rapid removal by reticuloendothelial system (RES), cell interactions or adsorption and intermembrane transfer.[5] Despite the fact that liposomes have been the hallmark of lipid nanoparticles (LNPs) for site specific delivery of therapeutics, there is a need to develop approaches for advanced control over drug release and drug delivery, which may not potentially load into liposomes. One of the reasons for this, apart from potential technological problems, is the non-availability of a ' cheap ' pharmaceutical liposome.

SLN and NLC have been introduced as potential attractive and marketable options due to their natural components.[6] SLNs and NLCs have been identified since 1990 as a substitute carrier system to liposomes, emulsions and polymeric nanoparticles.[7] Historical development of colloidal carrier system is illustrated in Figure 1. These LNPs have an average size of 40 to 1000 nm and a spherical morphology[8] and are composed of solid phase lipid and surfactant. Dispersed phase is solid fat, and surfactant is used as emulsifier. Lipid components of SLNs are solid at both body and ambient temperature [9] and can be highly purified triglycerides, complex glyceride mixtures or even waxes.[10] Surfactants are used in concentrations of about 0.5 to 5% to enhance stability. The proper selection of lipids and surfactants can affect physicochemical properties and quality of them such as particle size and drug loading.[11] Compared to liposomes, they have drug stability and prolonged release and they are safer than polymeric carriers because of avoidance of organic solvents in their production. As well as they have no problems with respect to large scale production. But the common disadvantages of SLNs are unpredictable gelation tendency and inherent low incorporation rates resulting from the crystalline structure of the solid lipid.[12,13]

NLCs have been introduced as the next generation of the SLNs at the ending of the 1990s to dominate the possible difficulties of SLNs.[14-16] NLCs improve the stability, capacity loading and prevent the drug expulsion during storage. They are detectable from SLNs by the composition of the solid matrix. lipidic

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phase in NLCs are contained both solid and liquid lipids at the room and ambient temperature.[17] Formless, imperfect and multiple types are three forms of NLCs which are discussed in the next part of paper.[18]

There are several production techniques for LNPs such as high pressure homogenization (HPH), solvent emulsification /evaporation, supercritical fluid extraction of emulsions (SFEE), ultrasonication or high speed homogenization[19-21] and spray drying.[22] Two processes of the HPH, hot and cold processes were developed. These are two basic production methods which in both, drug is dissolved or solubilized in the lipid being melted at around 5-10 °C above its melting point.[19]

SLNs and NLCs have remarkably wide range of properties which make them useful for parenteral, dermal, pulmonary and topical delivery of drugs. These products have been developed in order to reduce toxic side effects of the incorporated highly potent drugs and increase the efficacy of the treatment. As well as, they have presented good potential in gene transfer, cosmetic and food industry. However, because of mentioned limitations and difficulties related to them, the total number of products on the market is still limited.[23-26]

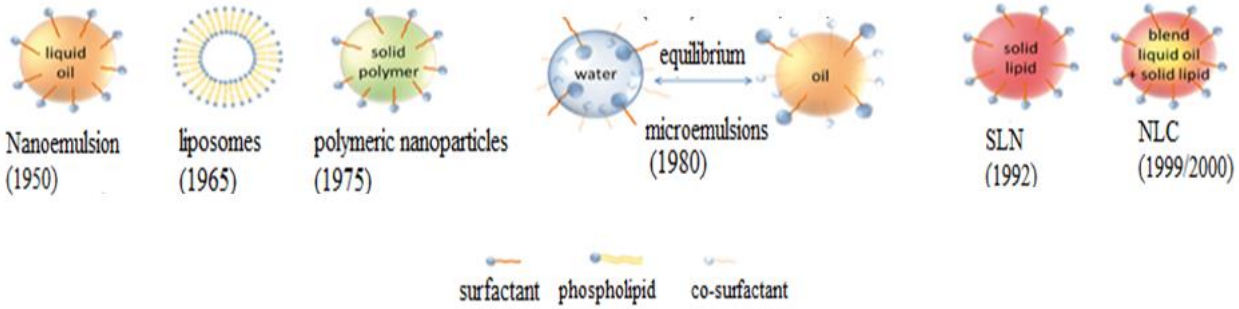

Figure 1. Schematic of historical development of colloidal carrier system.[26]

Definition and description of structural properties of SLNs and NLCs

SLNs were presented since 1990 as a substitute carrier system to liposomes, emulsions and polymeric nanoparticles.[17] They have an average size of 40 to 1000 nm and a spherical morphology that can be studied with TEM (Transmission electron microscopy) and SEM (scanning electron microscopy).[18] SLNs are composed of approximately 0.1 – 30 (% w/w) solid fat which is dispersed in an aqueous phase. Surfactants are used in concentrations of about 0.5 to 5% to enhance stability. The proper selection of lipids and surfactants can affect the particle size, long-term stability during storage, drug loading and behaviors of release.[19] Lipid components of them are solid at both body and ambient temperature.[23] The lipids which are used in preparation of SLNs include fatty acids, steroids, waxes, monoglycerides, diglycerides and triglycerides. Depending on method of preparation, SLNs may be used for both hydrophilic and hydrophobic drugs.[12,24]

Compared with other systems, SLNs have many benefits including ease of preparation, low cost, high-scale production, excellent physical stability, good release profile, chemical versatility, preparation in the absence of organic solvent, no toxicity of lipid carrier system, biodegradability of lipids, being cheaper than polymeric carrier, being easier to get approval and reliability and biodegradability of lipids.[25,27] Common disadvantages of SLNs are: Lipid particle growth, tendency to gelation, dynamics of polymorphic transitions, and their inherent low incorporation rate due to the crystalline structure of the solid lipid.[12,19,25,28-30]

Dependent of production method of SLNs, three models of drug incorporation into them have been reported which is described in detail in Table 1. These are including solid solution model, core-shell model (drug-enriched Shell) and core-shell model (drug-enriched core) which is shown in Figure 2.[25,31,32]

Table 1. Three models of drug incorporation into SLNs

Solid solution model	Core-shell model (drug-enriched shell)	Core-shell model (drug-enriched core)
Formation of this model in cold homogenization technique	Formation of this model in hot homogenization technique	Dispersion cooling leads to a supersaturation of the drug which is dissolved in the lipid.
Using no drug-solubilizing surfactant	Formation of lipid core at recrystallization temperature of lipid	Precipitation of drug in melted lipid
Drug dispersed in lipid matrix	Cooling of the obtained dispersion leads to re-partitioning of the drug to the lipid phase	Finally, further cooling lead to recrystallization of the lipid
There is a strong interaction between lipid and drug	Concentration of drug in surrounding membrane	Formation of drug-enriched core

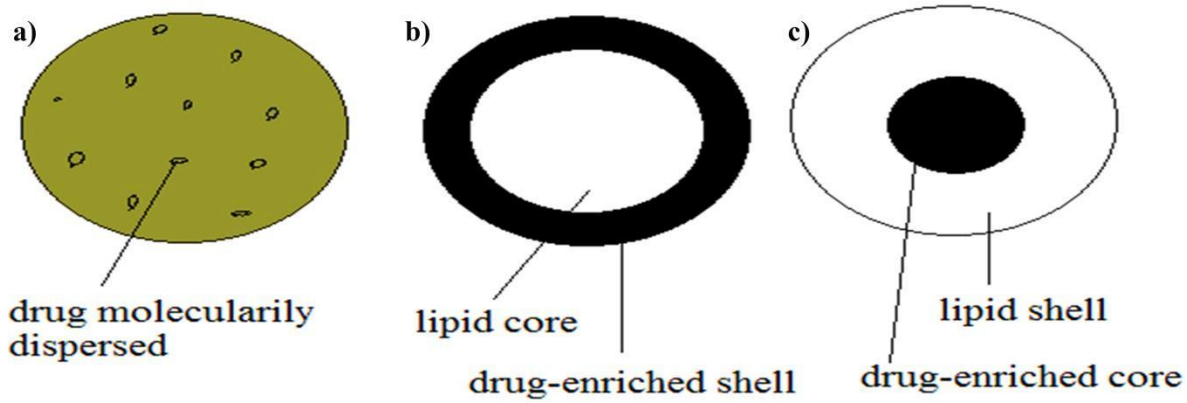

Figure 2. Schematic representation of drug incorporation models of SLNs. a) solid solution model, b) core-shell model (drug-enriched Shell), c) core-shell model (drug-enriched core).

In the next generation of the lipid nanoparticle, NLCs are modified SLNs in which lipidic phase is contained both solid (fat) and liquid (oil) lipids at ambient temperature.[33] In fact NLCs are modified generations of SLNs that presenting a mixture of solid and liquid phase (oil) forming a formless matrix, which improves the stability and capacity loading.[34] NLCs show contrasts with SLNs: more loading capacity for some drugs, some less water in the dispersion, prevent or minimize the drug expulsion during storage, but not reported significant difference between the biotoxicity of SLNs and NLCs. [17,32,33,35,36] Three forms of structure for NLCs have been presented which is shown in Figure 3. The first class is imperfect type in which solid and liquid fats (oil) are mixed in various lipid structures. Specific conditions in the crystallization procedure lead to an extremely disordered. Imperfect lipid matrix structure presenting gap between triglyceride fatty acid chains in crystal and thus increase the ability of the drugs for entering to the matrix. [37-39] The second class is formless type (non-crystalline matrix), this is a type of NLCs that has no crystalline structure and thus prevents the expulsion of loaded drug which is known as amorphous type. In this form, crystals are formed during cooling and for preventing from it, must be used certain lipids mixture.[39-41] The third class is multiple type: in this class drug solubility in liquid lipid is greater than in solid lipid, thus maintained from decomposition by solid lipid. This form of NLCs is similar to w/o/w emulsions.[27,42]

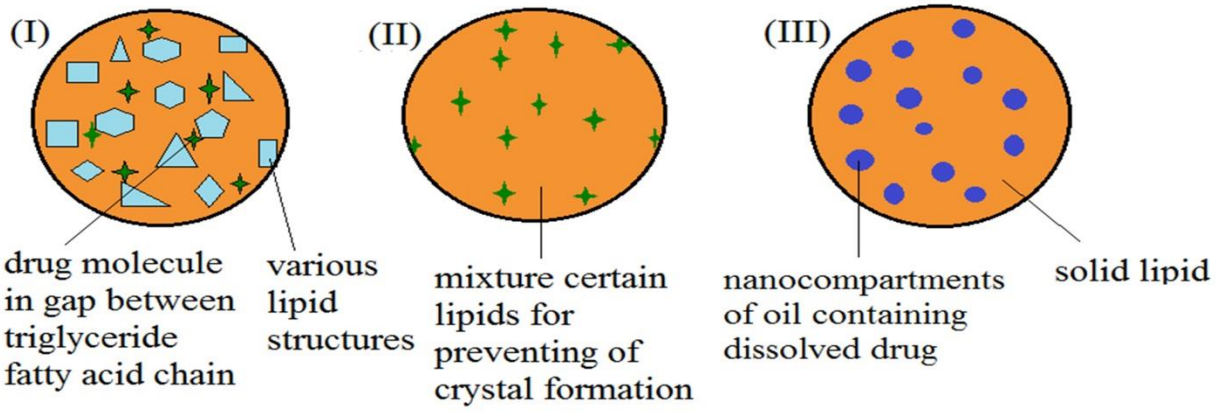

Figure 3. Structures of NLC. Class I (imperfect type), class II (formless type), class III (multiple type). To prevent drawbacks of SLN, the NLC should possess sufficient gap to better drug accommodation.[43]

Preparation of lipid nanoparticles

There are many systems for the production of LNPs. Commonly used methods for preparation of SLNs are high pressure homogenization at elevated or low temperatures (including hot homogenization and cold homogenization), solvent emulsification ,evaporation or diffusion, supercritical fluid (supercritical fluid extraction of emulsions (SFEE)), ultrasonication or high speed homogenization[19-21] and spray drying.[22]

High pressure homogenization (HPH)

HPH technology has emerged as an established and potent technique for production of lipid nanoparticles. In contrast to other techniques, this method for large-scale production of LNs also can be used. Two processes of the homogenization, hot and cold processes were developed. The pharmaceutical compound is dissolved or dispersed in the melted lipid before to the HPH, in both processes. High pressure (100–2000 bar) moves the fluid in the narrow gap in homogenizer. Average particle size

is in sub-micron region. Homogenization has several advantages including large-scale production, absence of organic solvent, improved product stability and improved loading of drugs, but specific high pressure and temperature conditions make challenges about its application.[2,44]

Hot homogenization

In this method, homogenization occurs at temperatures upper than melting point of lipid. Drug loaded lipid melt is dispersed in hot aqueous surfactants phase (isothermal) by mixing device (Ultra-Turrax) and leads to the formation of pre-emulsions. Because of the reduced viscosity at high temperatures, particle size becomes lesser mainly.[45,46] This technique is illustrated in Figure 4. Hot homogenization has three basic problems. The first is temperature-dependent degradation of the drug, the second is the drug penetrates into the aqueous phase during homogenization and the third is complexity of the crystallization step of the nanoemulsion leading to several modifications and/or supercooled melts.[14,47]

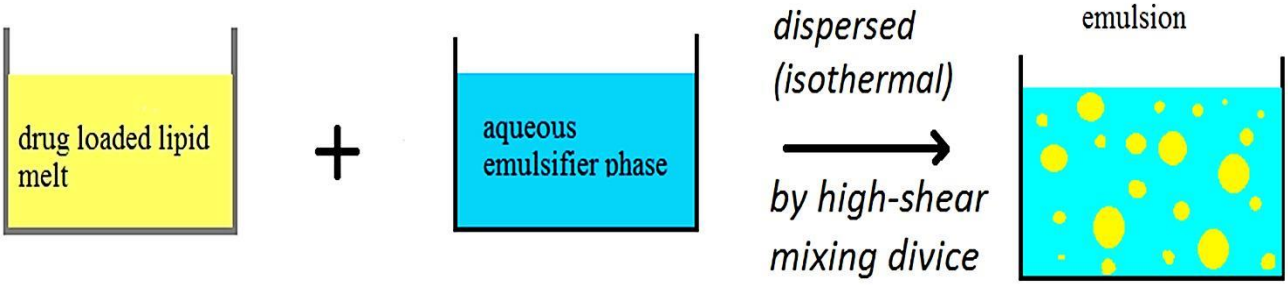

Figure 4. Hot homogenization technique for production of SLN[48]

Cold homogenization

Like the hot homogenization method, the drug is dissolved in the lipid melt, and then rapidly cooled by liquid nitrogen or dry ice. Milling leads to formation of nanoparticles in the range of 50-100 nm which are dispersible in a cold surfactant phase that form a pre-suspension. PHP is done at ambient temperature that leads to break the nanoparticles to SLNs. Cold homogenization technique has been expanded to resolve the problems of the hot homogenization technique[3,49] Schematic diagram of this method is given in Figure 5.

Solvent emulsification /evaporation

In this method, the lipid is dissolved in a water-immiscible organic solvent. Next an emulsion in an aqueous phase containing surfactant is formed. To remove the solvent from the emulsion, evaporation under reduced pressure is used. Evaporation leads to the dispersion of nanoparticles in the aqueous phase (using lipid precipitation process in the aqueous phase). Unlike cold homogenization, this method will not enter to any thermal stress, but the organic solvent which is used in this method is a disadvantage. Particle size can vary according to the solid lipid and surfactant.[41,50]

Supercritical fluid extraction of emulsions (SFEE)

SFEE is a relatively novel approach for SLN preparation. This method uses a supercritical fluid such as carbon dioxide for solvent extraction from o/w emulsions. Carbon dioxide is a good option, but it should be noted that it can't dissolve many of the drugs. Therefore supercritical antisolvent precipitation (SAS) can be an alternative method to SFEE.[51,52]

Ultrasonication or high speed homogenization

One of the methods for the production of LNPs is ultrasonication or high-shear homogenization. The aqueous phase containing a large amount of surfactant, and lipid phase is dispersed in this phase. The high amount of surfactant will be considered as a disadvantage. Another disadvantage of this method is that it doesn't produce a narrow particle size distribution, thus leading to instability during storage. This technique uses from the simple instruments that can be found in every lab unlike hot and cold homogenization.[53,54]

Spray drying

This system is a substitute to lyophilization method that leads to the production of pharmaceutical product from aqueous SLN dispersion. Spray drying is cost effective method rather than lyophilization, but is not used for the production of lipids commonly. Because the high temperatures and shear forces used in this way, leads to particle aggregation. According to previous studies, lipids with melting point greater than 70 °C are suitable for spray drying. [55]

Applications of lipid nanoparticles

SLN and NLC have remarkably wide range of application and have shown greatly to control the skin penetration of several actives, delivery of food and drugs, cosmetics and other applications.[26]

Oral drug delivery applications

Oral drug administration is common and preferred route due to good patient compliance, non-invasiveness and therapeutic success, but poorly water-solubility of drugs is limiting step for the absorption of them. Thus an approach is needed to improve the bioavailability of drugs. Lipid-based delivery systems in the recent decades have shown many advances for this purpose. These systems include a wide range of formulations such as self-nanoemulsifying drug delivery system (SNEDDS), self-microemulsifying drug delivery system

(SMEDDS), nanoemulsions, SLNs and NLCs. Since in these systems, drug is dissolved in the lipid thus makes the potential for improving the bioavailability of poorly soluble drugs in water, especially lipophilic drugs. In fact, these systems can increase dissolution of drug, residence time and lymphatic uptake. A good thing is that toxicity has not been observed in most cases.[56-59]

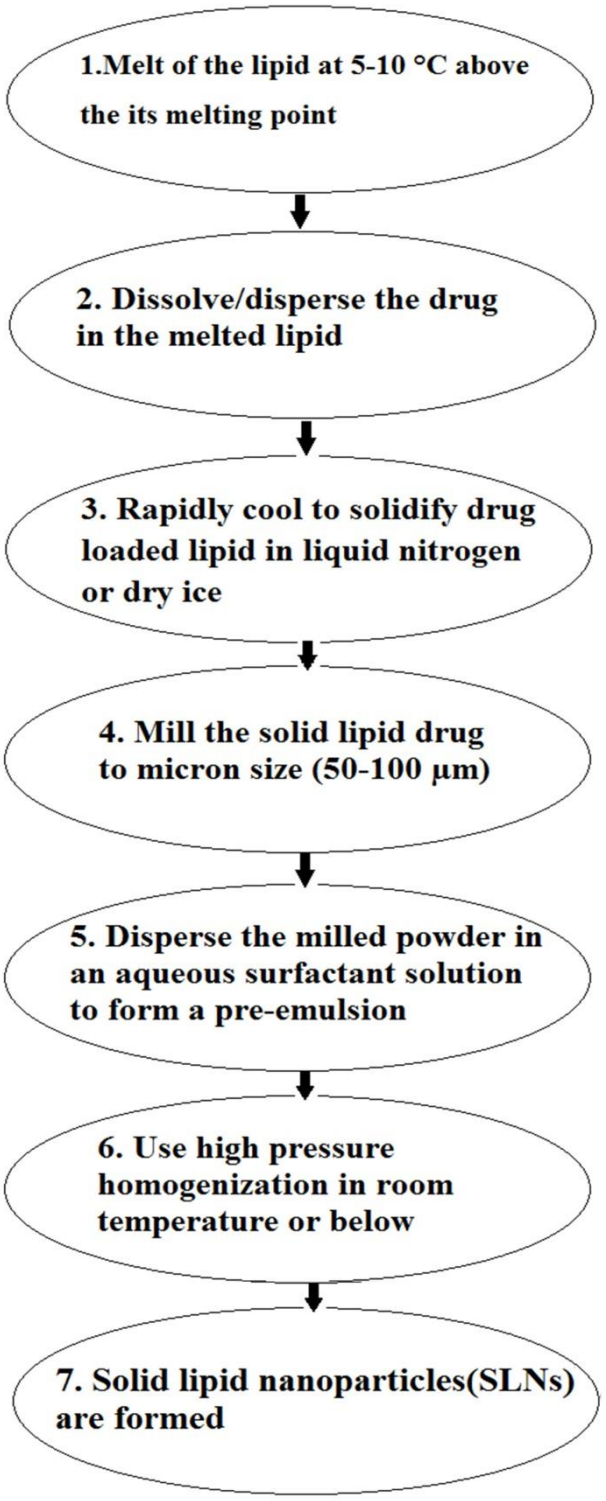

Figure 5. Schematic diagram of cold homogenization method for preparation of SLNs

Pulmonary drug delivery applications

LNPs easily incorporated into carriers which inhaled to the lungs, therefore able to provide a deep lung deposition, good adhesion and elongated retention in the lung. Also due to improved and prolonged therapeutic effects, SLNs and NLCs have a longer dosing interval and better compliance for patients. They are typically particulate systems for various drug delivery applications. Advantages of drug release of fat in the lungs including: control of the release profile, prolonged release, faster in vivo degradation and better tolerability compared to particles made from some polymeric materials such as PLA or PLGA. Pulmonary delivery of SLNs is not widely accepted because of toxicity issues but when the physiologic lipids are used, is estimated to be safer than polymer-based systems. Dry powder formulations or aqueous suspensions of SLNs can be used for pulmonary drug delivery. Many studies are available about SLNs as local delivery carriers or as systemic delivery carriers for small molecules and for macromolecules respectively by pulmonary administration.[60-63]

Gene transfer applications

LNPs penetrate to biological membranes effectively through receptor-mediated pathway because lipids are the most important components of cell membranes. Thus enhance the uptake of genetic compounds.[64,65] The delivery of some bioactive to particular sites in the body and their release behavior is directly dependent to particle size.[66] The achievement of gene therapy (with DNA and RNA transfer) depends on the new bioactive delivery techniques. While 1980; more than 400 clinical studies in gene therapy have been reported. Delivery vectors are used in gene transfer due to restricted ability of naked DNA transfer to cells owing to propensity to enzymatic degradation.[67-71] Cationic SLNs are interesting and proper nonviral gene delivery vector for systemic delivery. SLNs directly bond with DNA and can be used for gene transfection. Genospheres (such as cationic SLNs) have large potential for targeted gene delivery. Genospheres generally carry materials such as plasmid DNA, DNA and other nucleic acids. Three issues are important about them: composition of cationic SLN, their ability to condense DNA and transferring of nucleic acid to cells.[59,66] NLCs can be effectively used as novel nonviral gene transfer vector that offers a promising approach for gene therapy.[72]

Cosmetic applications

LNPs such as SLNs and NLCs are one of the excellent vehicles for cosmetic and dermatological application. They have some characteristics which make them talented carriers for cosmetic applications for instance protection of sensitive compounds against chemical degradation[15] and enhancement the water content of the skin.[13] The use of LNPs as carriers for sunscreens, anti-acne and anti-ageing actives has been investigated. In fact, due to the high control behaviors of LNPs on skin

penetration of active substances, they have UV-blocking and skin hydration behavior. In cosmetic products, reduction of the desire to scratch and skin damage is important. Since these formulations bear a resemblance to skin structure, there is no disruption and toxic effect when used topically.[17]

Food applications

LNPs are of particular interest to food manufacturers as novel delivery systems for encapsulation of bioactive compounds. LNPs are excellent potential carriers for sensitive compounds in food industry because they improve the industrial and the nutritional quality of a lipid containing food. Quality of them is affected by the lipid oxidation at storage and processing steps. Therefore must use antioxidants to prevent this process. Examples of active substances enclosed in LNPs for food industry are Beta-carotene, Lutein and Lycopene.[11,73-76]

Conclusion

In summary, SLNs are very complex system with obvious advantages and disadvantages compared to other colloidal carriers. Due to the stability and drug expulsion problems of SLNs, the NLCs were emerged. Based on the composition and organization of lipids and drugs in the particles, a wide collection of structural forms have been illustrated for SLNs and NLCs. The extremely unordered lipid matrix structured of NLC, enhanced drug encapsulation and stability, and also presenting good release profile made them popular in nano pharmaceutical research field and other applications. They are produced by different advanced methods. The preparation of these systems as well as of other lipid nanoparticle is possible and practicable in laboratory and on large scale. Additional efforts are needed to know the dynamics of LNPs on a molecular phase in vivo and in vitro.

Ethical Issues

Not applicable.

Conflict of Interest

The authors report no conflicts of interest.

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