

Lipid Nanostructured Particles as Emerging Carriers for Targeted Delivery of Bioactive Molecules: Applications in Food and Biomedical Sciences (An Overview)

Patricia MUNTEAN¹, Carmen SOCACIU*^{1,2}, Mihai Adrian SOCACIU^{2,3}

¹Faculty of Food Science and Technology, University of Agricultural Sciences and Veterinary Medicine, 3-5 Manastur Street, 400372 Cluj-Napoca, Romania

²R & D Center for Applied Biotechnology, Proplanta SRL Cluj-Napoca, Romania

³University of Medicine and Pharmacy "Iuliu Hatieganu" Cluj-Napoca

*corresponding author: carmen.socaciu@usamvcluj.ro

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Abstract

Lipid nanoparticles are getting a growing scientific and technological interest, worldwide. Either Solid Lipid Nanoparticles (SLNs), Nanostructured Lipid Carriers (NLCs), Lipid Drug Conjugates (LDCs) or Polymer-Lipid Nanoparticles (PLNs) have been produced and investigated last years, being recommended as emerging carrier systems for many food and biomedical applications. An overview of the last publications, mainly since 2017 is presented, underlying the most important methods and techniques used for their preparation (e.g. high shear homogenization in hot and cold conditions, ultrasound assisted melt emulsification) as well techniques applied for measuring the size, calorimetric properties, zeta-potential, etc. Most relevant data related to the use of food-grade ingredients and designed lipid nanoparticles as delivery systems for organic and inorganic bioactive molecules in food or packaging's are presented. The major reason for this trend in food science is the aim to overcome problems associated with the low bioavailability of many lipophilic bioactive compounds which are claimed to bring benefits to human health (carotenoid or anthocyanin pigments, sterols, vitamins). Finally, the recent applications of different formulas of lipid nanoparticles as drug carriers for *in vitro* experiments or for *in vivo* therapy (oral, parenteral or transdermal formulas) are presented.

Keywords: solid lipid nanoparticles, nanostructured lipid carriers, targeted delivery

Introduction

Since the beginning of the 1990s the lipid nanoparticles are getting a growing scientific and technological interest, worldwide. Nowadays Solid Lipid Nanoparticles (SLNs), Nanostructured Lipid Carriers (NLCs) and Lipid Drug Conjugates (LDCs) have been already produced and investigated as carrier systems for many applications. Lipid nanoparticles were developed as an alternative to former carriers, such as polymeric nanoparticles, self-emulsifying delivery systems, liposomes, mi-

cellar solutions microemulsions, are still exploited as carriers for bioactives' delivery (Rawat, 2011, Socaciu, 2019). Recently it was reviewed an overview of different preparation methods of polymeric and novel lipid-based (niosome and solid lipid) nanoparticles (Ghasem, 2018).

Solid Lipid Nanoparticles (SLNs) are typically spherical structures with an average diameter between 10 and 1000 nm, possesses a solid lipid core matrix that can solubilize lipophilic molecules and is stabilized by a surfactant

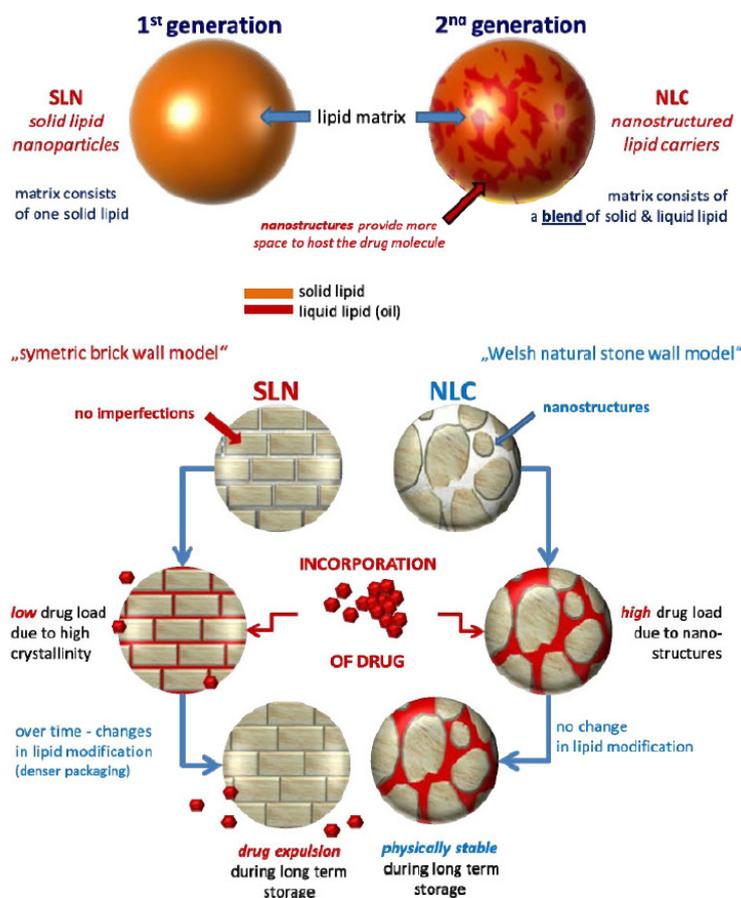


Figure 1. Comparative structure and properties of the lipid nanoparticles SLN vs. NLC (from Patel, 2013)

(Fig.1). The core lipids can contain triglycerides, fatty acids, waxes and mixtures of these molecules. The lipid core is stabilized by surfactants (emulsifiers), e.g. diglycerides or monoglycerides, short chain fatty acids, sterols (cholesterol), phospholipids, sphingomyelins, bile salts (sodium taurocholate) (Mehnert, 2001; Singh, 2018).

The development of new formulas for SLNs is one of the emerging fields of lipid nanotechnology with several potential applications in food, cosmetic or pharmaceutical research, drug delivery or clinical medicine. Due to their size-dependent properties, lipid nanoparticles offer the possibility to develop new prototypes or therapeutics with increased bioavailability along with controlled and site specific drug delivery. SLNs are well tolerated *in vivo* due to their composition containing physiological, similar lipids (Mashghi, 2013).

NLCs were primarily considered for the delivery of lipophilic drugs but their suitability for hydrophilic drugs is also well established. The biocompatible nature of lipids is responsible for

NLC development as a promising drug delivery, having superior characteristics over other lipid formulations (Salvi, 2019).

Nanostructured Lipid Carriers (NLCs) are modified SLNs with improved loading capacity, drug stability and preventing the drug leakage. Fig.1. represents the structure of SLN in comparison with NLC, as well the delivery ways. The NLCs include a blend of solid and liquid lipids which results in a partially crystallized lipid system and imparts many advantages over SLNs 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 their easier preparation, the feasibility of scale-up, biocompatibility, non-toxicity, enhanced targeting efficiency and the possibility of site-specific delivery via various routes of administration (Qianwen, 2017).

The lipid-drug conjugates (LDCs) have the therapeutic actives chemically bound to a lipid

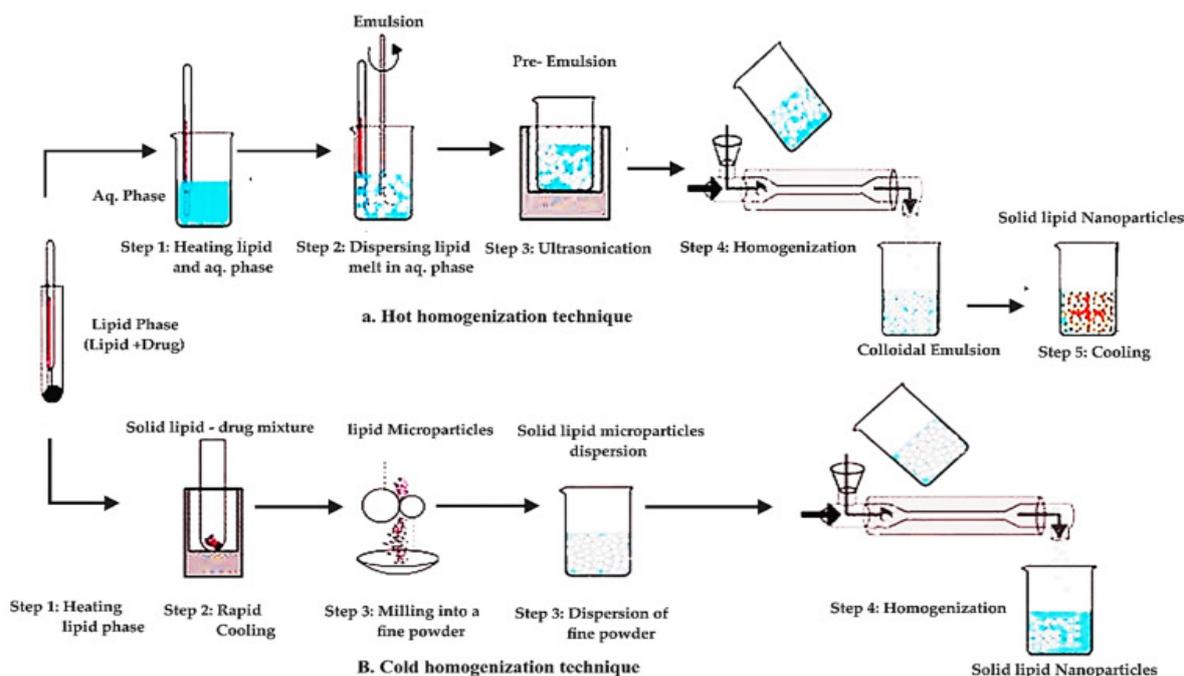


Figure 2. Techniques and steps used to prepare SLNs: hot (a) and cold (b) homogenization (from Ganesan and Narayanasamy, 2017)

moiety like fatty acids or phospholipids, fabricated in nano-size and can be prepared in order to increase the drug loading and hence prevent leakage of a highly polar drug from a lipophilic matrix. Recently, it was reviewed the preparation of lipid drug conjugates, processed as nanoparticles, their characterization and different applications, as a suitable drug delivery approach (Piya, 2017).

Polymer-based nanoparticles are also important components for drug delivery. These nanoparticles can effectively direct drug delivery to specific targets and improve drug stability and controlled drug release. Polymer-Lipid Nanoparticles (PLNs), represent a new type of carrier that combines liposomes and polymers, have been employed in recent years. These nanoparticles possess the complementary advantages of polymer nanoparticles and liposomes. PLNs have core-shell structures, the polymer core providing a stable structure, while the phospholipid shell offers good biocompatibility. The two components increase the drug encapsulation efficiency rate, facilitate surface modification, and prevent leakage of water-soluble drugs. Recently (Qianwen, 2017), published an overview about the current state of development for the polymer nanoparticles, NLCs' and PLNs' including many useful informations about such drug delivery systems.

Recently, there were reviewed new data about NLCs, focused on their structure, the various fabrication techniques and the characterization techniques which are critical in the development of a suitable and stable formulation. The same 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 (Archana, 2018).

Methods of preparation

Recently, there were reviewed the main methods of preparation for SLNs/NLCs, the recommended excipients, their characterization and significant findings related to their stability and oral administration (Ganesan and Narayanasamy, 2017).

Initially used for the production of solid lipid nanoemulsions, the method applied to obtain SLNs is named generically "High shear homogenization" (HSH) and involve high pressure homogenization which pushes the liquid (hot lipid mixture) with high pressure (100-2000 bar) through a narrow gap ranging a few microns. The fluid accelerates to a very short distance at very high viscosity, this high shear stress and cavitation forces disrupt the particles down to submicron range. As low as 5% to as high as of 40% lipid content has been

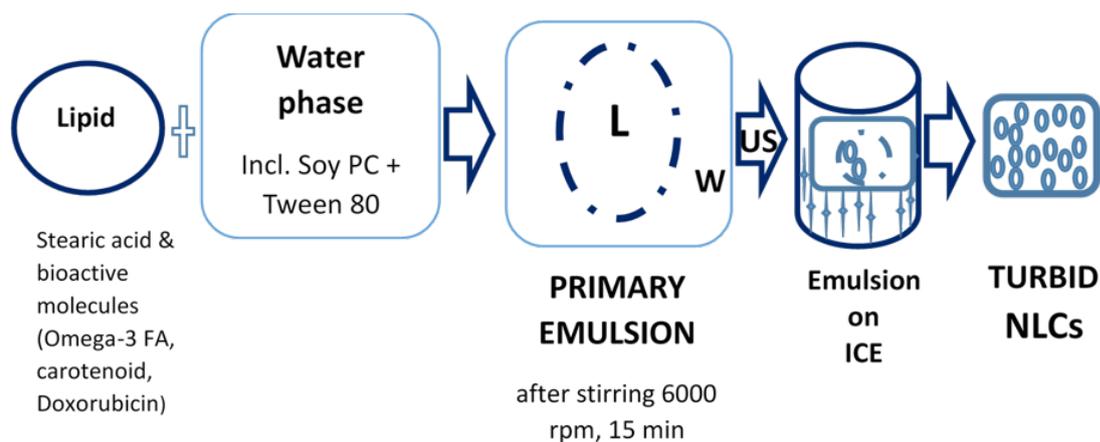


Figure 3. Melt-Emulsification & Ultrasonication Method to obtain NLCs (Sreedhar et al., 2019)

investigated. Two general approaches to obtain SLNs by HSH are hot homogenization and cold homogenization (Mehnert and Mader, 2001). Fig. 2 presents comparatively the main steps of hot (a) and cold (b) homogenization to obtain SLNs.

The hot homogenization is generally carried out at temperatures above the melting point of the lipid. A pre-emulsion of the drug loaded lipid melt and the aqueous emulsifier phase (same temperature) is obtained by high shear mixing device. The product is a hot oil/water emulsion, its cooling leading to the crystallization of the lipid and the formation of SLNs. Smaller particle sizes are obtained at higher processing temperatures due to lower viscosity of the lipid phase. However, high temperature may increase the degradation rate of the drug and the carrier. Increasing the homogenization temperature or the number of cycles often results in an increase of the particle size due to high kinetic energy of the particles. Generally, 3-5 homogenization cycles at a pressure of 500-1500 bar are used (Mehnert and Mader, 2001; Jenning et al., 2002).

The cold homogenization has been developed to overcome the temperature-related degradations, loss of drug into the aqueous phase and partitioning associated with hot homogenization method. Unpredictable polymeric transitions of the lipid due to complexity of the crystallization step of the nanoemulsion resulting in several modifications and/or super cooled melts. Here, drug is incorporated into melted lipid and the lipid melt is cooled rapidly using dry ice or liquid nitrogen. The solid material is ground by a mortar

mill. The prepared lipid microparticles are then dispersed in a cold emulsifier solution at or below the room temperature. The temperature should be regulated effectively to ensure the solid state of the lipid during homogenization. However, compared to hot homogenization, larger particle sizes and a broader size distribution are typical for cold homogenization samples (Ekambaram et al., 2012).

Recently, the nano spray-drying (NSD) technique was considered as a fast, innovative one-step method to produce SLNs as a dry powder starting from a lipid/leucine oil/water emulsion. In a specific application, Compritol was chosen as wall-forming lipid and Rapamycin as a model drug to be loaded into SLNs and Lutrol F68 as surfactant using the high-shear homogenization method. A yield of 51% was achieved to obtain a SLNs population of a size around 150nm (Glaubitt, 2019).

Another method, named Supercritical Assisted Injection in a Liquid Antisolvent (SAILA) was also proposed for the production of SLNs containing soy lecithin, cholesterol, stearic acid and acetone or ethanol as solvents. SLNs with mean dimensions of 158 - 326 nm were obtained for soy lecithin particles, 151 - 207 nm for cholesterol and 364 - 462 nm for stearic acid particles. All the suspensions were stable over 30 days of observation (Trucillo, 2019).

Melt-Emulsification combined with Ultrasonication Method was recently reported (Sreedhar et al., 2019). Fig. 3 presents the most important steps to obtain NLCs by using this method.

Table 1. Modern methods and techniques used to determine different physico-chemical properties of lipid nanostructured particles.

Physico-Chemical properties	Methods/Techniques
Shape and surface morphology	Transmission electron microscopy (TEM) Scanning electron microscopy (SEM) Phase contrast optical microscopy (PCM) Atomic force microscopy (AFM) Freeze fracture microscopy
Size and size distribution	Dynamic light scattering (DLS) Electron microscopy (SEM/TEM) Optical microscopy Photon correlation spectroscopy (PCS)
Electrical surface potential and and electrophoretic mobility	Zeta potential measurement Laser light scattering technique
Calorimetric properties	Differential Scanning Calorimetry (DSC)
Surface hydrophobicity	Hydrophobic interaction chromatography Two-phase partition Contact angle measurement X-ray photoelectron spectroscopy Synchrotron radiation X-ray (SAX)
Density	Gas pycnometry
Molecular weight	Gel permeation chromatography (GPC)
Rheology	Viscosimetry
Release <i>In vitro</i>	Dialysis membrane dissolution test

High-pressure homogenization was successfully applied to prepare NLCs which incorporate Nimodipine. Their morphology (spherical shape of 70 nm with a smooth surface) was observed by a transmission electron microscope and the powder by X-ray diffraction, differential scanning calorimetry, and Fourier transform infrared spectroscopy, respectively. The preparation had a high efficiency of 86.8%, the relative bioavailability of Nimodipine -loaded NLCs being 160.96% relative to free Nimodipine suspensions, providing a promising nanoplatform for hydrophobic drug delivery (Teng, 2019).

Charcosset et al. (2005) presented another process for the preparation of SLN using membrane contactor. Shortly, the lipid phase was melted and pressed through ceramic membrane pores (0.1-0.45 microns) and SLNs were formed by cooling to room temperature.

Recently, Gao and McClements (2016) applied the the phase inversion temperature method to produce SLNs using a Surfactant/oil/water

system (Brij 30, C₁₂E₄)/oil (octadecane)/water, maintained at a temperature above the phase inversion, and followed by cooling below the lipid nanoparticle crystallization point.

The detailed knowledge of the structure of the lipid nanoparticles was highlighted recently, as well the design of these nanocarriers, proposing solutions for their formulation (Gordillo-Galeano, 2018).

Evaluation of physico-chemical properties

The successful applications of SLNs, NLCs or PLNs are related to their stability, physicochemical properties, mainly determined by the components (e.g. lipids, emulsifiers) and their compatibility, by excipients and the preparation methods.

Table 1 include the main methods used to characterize the structure of SLNs and NLCs (Ganesan, 2017).

Recently, Talele (2018) prepared biocompatible SLNs with glycerol monostearate as lipid and varying combinations of sodium deoxycholate

and cholate (bile salts to lipid ratio 8% w/w) as emulsifiers. The detailed characterization was performed using a combination of light scattering, microscopic, calorimetric, and spectroscopic techniques. It was seen that different compositions of bile salts yield nanoparticles with different sizes (from 487 to 652 nm), depending on the deoxycholate per cholate ratios.

Differential scanning calorimetry (DSC) has emerged as a helpful technique both to characterize SLNs obtained by phase inversion temperature, their capability as drug delivery systems and interactions with bio-membranes. DSC Studies were applied also on (Montenegro *et al.*, 2011; Gao and McClements, 2016; Montenegro, 2018).

When compared idebenone (IDE)-loaded SLN interactions with bio-membranes assessed by DSC using *in vitro* interactions with multi-lamellar liposomes as a model of bio-membrane, the results suggests the possibility of qualitatively predicting *in vitro* IDE skin penetration from IDE-loaded SLN utilizing the calorimetric parameters obtained from interaction experiments between the carriers under investigation and a model of bio-membrane. Suspensions of SLNs stabilized with emulsifiers have been extensively investigated since 3 decades as drug carriers, although details of their ultrastructure are poorly defined. Previously, a novel microwave-assisted microemulsion-based technique to prepare SLNs was reported. To understand the detailed internal structure of these SLNs, ultra-small angle neutron scattering (USANS) and small angle neutron scattering (SANS) experiments were conducted on suspensions of hydrogenated stearic acid SLNs stabilized with hydrogenated Tween 20 surfactant in D₂O (Shah, 2019).

Applications in food science

Nowadays, in food science and technology, edible coatings incorporated with nanostructures as systems of controlled release of flavors, colorants and/or antioxidants and antimicrobial substances, are used for thermal and environmental protection of active compounds. Such functionalized nanostructures have the benefit of incorporating natural substances obtained from the food industry that are rich in polyphenols, dietary fibers and antimicrobial substances. In addition, the polymers employed on its preparation, such

as polysaccharides, solid lipids and proteins that are low cost and developed through sustainable processes, are friendly to the environment. Recently, a review was dedicated to the description of materials commonly used in the preparation of these nanostructures, the main ingredients used for functionalization and preparation of edible coatings, as well as the advances that these structures have represented when used as controlled release systems, increasing the shelf life and promoting the development of new products that meet the characteristics of functionality for fresh foods ready to eat (Gonzalez-Reza, 2018).

Notable progress has been achieved in the preparation of nanoformulas containing selected dietary polyphenols (from crude extracts or standardized fractions) (Antal, 2017) or

beta-carotene-loaded NLCs stable over time and offer a sustainable system for new functional foods (Pezeshki, 2019).

In another study, the formation of lipid nanoparticles (570-780 nm) with low (corn and olive oil) or high temperature melting lipids (cocoa butter and hydrogenated coconut oil) stabilized with Tween 80 was achieved. This work demonstrated the potential of lipid nanoparticles to protect lipophilic bioactive compounds with a high digestibility and bioaccessibility (Salvia-Trujillo, 2019).

A SLN nanoparticulate delivery system was prepared for developing a food grade carrier for (-)- epigallocatechingallate (EGCG), the major constituent in green tea. EGCG-SLNs were produced by the hot homogenization method, had an average particle size of 108-122 nm, with an encapsulation efficiency up to 68.5%. Such food grade SLNs protected successfully EGCG along the storage period as well as under the adverse conditions at neutral pH values. (Shtay, 2019). Chitosan, an excipient having positive characteristics such as muco-adhesiveness and ability to open epithelial-tight-junctions was functionalized with lipophilic stearyl groups and dopped with curcumin, as a model drug. This nanocomplex was characterized and tested *in vitro*. The curcumin entrapment in the complex prolonged the permanence of drug in the systemic circulation, as compared to curcumin solution (Chirio, 2018). The results of another study shows the efficacy of curcumin-loaded NLCs in the treatment of CNS diseases. (Malvajerd, 2019).

Nanoencapsulation of α -tocopherol (α -TOC) by blending sodium oleate and rebaudioside A was successfully prepared by self-assembly method under mild conditions, the loading capacity of α -TOC was 30 wt% of sodium oleate. The freeze-dried complex had great stability under ambient conditions and is generally recognized as safe (GRAS) ingredient with great potential to supplement α -TOC in food as well in cosmetic products (He, 2018).

The development of engineered nano-sized materials (ENM) produced with food-grade ingredients and designed as delivery systems for organic and inorganic materials has gained increasing interest. The major reason for this trend is the aim to overcome problems associated with the low bioavailability of many bioactive compounds (BC) which are usually claimed to benefit human health. In this review, outcomes of studies investigating the potential bioavailability enhancement of BC using ENM as delivery systems are summarised and discussed. It focuses on *in vitro* and *in vivo* studies carried out with ENM produced with food-grade materials and designed for the delivery of vitamins, other secondary plant metabolites and minerals. Furthermore, the physical and physicochemical aspects governing the preparation of the systems, the loading of the BC, the stability of the delivery systems in food applications and finally the release of the BC in the gastrointestinal tract are also considered. The mechanisms leading to an enhanced bioavailability are based on (i) improved solubility of the BC under gastrointestinal conditions, (ii) the protection of the BC from the chemical conditions in the gastrointestinal tract (GIT), (iii) the controlled release within the GIT or (iv) an improved transfer through the intestinal wall. The main outcome of the review is that particle size, surface properties and physical state of the ENM are key parameters to be controlled aiming at an enhanced nutritional value of food materials. Furthermore, the bioavailability classification scheme (BCS) can help to understand the efficacy of different ENM for the delivery of specific BC (Oehlke, 2014).

Applications in biomedical sciences

Nanosciences offers an operative tool in terms of using environmental friendly nanomaterials with increased stability, good carrier properties,

high bioavailability, targeting, and controlled release of natural bioactives or synthetic drugs while protecting active constituents against physico-chemical alterations. The interest of the scientific community in the field of nanosized delivery of bioactive compounds is demonstrated by the exponential growth of the publications in this field the last two decades, SLNs and NLCs being increasingly used as drug delivery systems. There are many underexplored capacities of this field with relevance for the biomedical/pharmaceutical market.

A recent review reveals the methods of preparation, characterization and application of several nanoparticles drug delivery system (Sharma, 2018) for clinical applications (Huilung, 2018). Recently a review summarized the therapeutic potential of SLNs and NLCs, considering researches and patents on their administration via different routes and their preparations in the pharmaceutical market (Uner, 2017).

SLNs have recently acknowledged as a novel systems to oral and parenteral drug delivery. They combine the advantages of lipid emulsions and a polymeric nanoparticles, improving the temporal and *in vivo* stability comparative to the conventional drug delivery approaches (Mehnert et al., 2001). SLNs combine numerous advantages over the other colloidal carriers i.e. incorporation of lipophilic and hydrophilic drugs, in non-toxic carrier, avoidance of organic solvents in their preparation, possibility of controlled drug release and drug targeting, increased drug stability and no problems with respect to large scale production.

A recent study has demonstrated the use of SLNs as a platform for oral delivery of the mineral iron, by incorporating the hydrophilic molecule ferrous sulphate (FeSO_4) in a lipid matrix containing stearic acid (Zariwala, 2013). The use of SLNs doped with drugs is developing, using different administration routes, including oral, parenteral, transdermal, ocular, nasal, respiratory ways (Uner, 2017). Their preparation avoids organic solvents, protect sensitive drug molecules from the outer environment (water, light) and offer controlled release characteristics and high bioavailability (Seyfoddin, 2010). SLNs are especially useful in ocular drug delivery as they can enhance the corneal absorption of drugs and improve the ocular bioavailability of both hydrophilic and lipo-

philic drugs. Another advantage of SLNs is their stability during autoclave sterilization, a necessary step towards formulation of ocular preparations (Lide, 2015)

The SLNs and NLCs are also of great importance in skin cargo delivery and have vast application in current cosmetic formulations with improved the physiochemical stability of the skin based cosmetic products. They can be added to current cosmetic formulations without any significant problem due to their physical stability and compatibility with other ingredients. (Khezri, 2018).

Since most of the sunscreen formulations contain chemicals or synthetic molecules, nowadays, researchers are mainly focusing on herbal formulations. Silymarin, as natural flavonoids with excellent antioxidant properties was incorporated in SLNs by micro-emulsion method, the glyceryl monostearate being used as lipid, and Tween 80 as an emulsifier. The SLNs were evaluated for drug entrapment, particle size and morphology, zeta potential, and polydispersity index. The silymarin-SLNs dispersion was formulated into sunscreen cream and evaluated for various parameters, such as extrudability, viscosity, spreadability, drug content, *in vitro* drug release, *ex vivo* permeation of drug, *in vitro* and *in vivo* sun protection factor determination, *in vivo* skin irritation test, and accelerated stability studies. The results suggested that the sunscreen containing silymarin SLNs exhibited better photoprotective action. (Gladyston, 2018).

A recent review presented the benefits and future perspectives of different lipid nanocarriers used in drug delivery the oral route of delivery being considered to be the most favorable route with the highest patient compliance (Nabi, 2019). Another recent review compiles the basic know how about the phospholipids and the mechanism through which it improves the bioavailability of drugs. The increase in number of recent reports involving the utilization of drug-phospholipid complex to improve oral bioavailability of drugs thus explains how vital the strategy is for a successful oral delivery (Kuche, 2019).

Lipid nanoparticles (LNP) have specifically come up for dermal, transdermal, mucosal, intramuscular and ocular drug administration routes in the last twenty years. However, they need to be processed as semi-solid formulations such as LNP-hydrogel composites to turn into versatile drug delivery systems able to provide precise

spatial and temporal control of active ingredient release. Recent developments in the formulation of lipid nanoparticle hydrogel composites are highlighted, including examples of successful encapsulation and release of lipophilic drugs through the skin, the eyes and by intramuscular injections. In relation to lipid nanoparticles, a specific emphasis has been put on the LNP key properties and how they influence their inclusion in the hydrogel. Polymer matrices include synthetic polymers such as poly(acrylic acid)-based materials, environment responsive (especially thermo-sensitive) polymers, and innovative polysaccharide-based hydrogels. The composite materials constitute smart, tunable drug delivery systems with a wide range of features, suitable for dermal, transdermal, and intramuscular controlled drug release (Desfrancois, 2018).

In vitro biocompatibility and Photodynamic Therapy (PDT) were performed using L929-fibroblasts cell line and A549 cancer cell line and melanoma BF16-F10, respectively. PDT evidenced the antitumor efficacy of Oleic Acid 40% (NLC 40) with reduced cancer cell viability demonstrating that the presence of OA in the NLC seems to potentialize this antitumor effect. According to the results obtained, the systems developed may be promising for the incorporation of CIA1Pc in the treatment of skin cancer by photodynamic therapy (Almeida, 2018). Another review discusses the rationale behind the use of nanotechnology-based strategies for rectal drug delivery and provides a critical overview on the various types of nanosystems proposed so far (Melo, 2018).

In order to reduce enzymatic degradation and thereby improve the stability of SLNs in the gastrointestinal tract (GIT), two amphiphilic macromolecular materials of N-stearyl-N-trimethyl chitosan (STMC) and N-linoleoyl-N-trimethyl chitosan (LTMC) were fabricated as emulsifier to modify SLNs. Both STMC-SLNs and LTMC-SLNs had excellent gastrointestinal stability and efficacy (Qiu, 2018).

A recent review is investigating Transdermal drug delivery (TDDS) applications, physical and chemical characteristics of these systems, their routes of penetration through the skin, and summarizes recent advances using these systems in treating conditions such as alopecia, wound healing, psoriasis, and melanoma (Carter, 2019).

Conclusions

Last years we assist to a tremendous interest for preparing natural, biocompatible and non-toxic nanoparticles, containing mixtures of different edible lipids, emulsifiers and bioactive molecules, stable, bioavailable and beneficial for human and animal health. Beside the increasing number of available preparation recipes and technological solutions, the lipid nanostructured particles are investigate for their size and many other physico-chemical properties which confer stability and improved targeted delivery. Their capability to act as drug- or bioactives' carriers with biomedical applications was proved in many experiments. Food science and technology will certainly more and more benefit of these new systems by creating innovative mixtures able to increase the accessibility and bioavailability of many lipophilic molecules to be stabilized and keeping their bioactivity in food matrices.

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