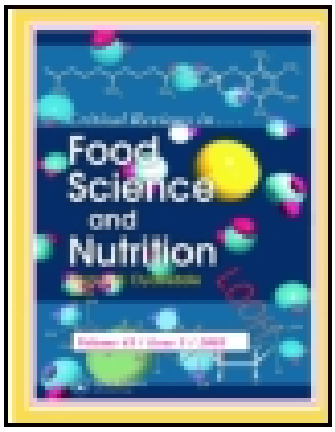

Critical Reviews in Food Science and Nutrition
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/bfsn20

Solid Lipid Nanoparticles as Oral Delivery Systems of Phenolic Compounds: Overcoming Pharmacokinetic Limitations for Nutraceutical Applications

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Accepted author version posted online: 20 Jul 2015.

Solid lipid nanoparticles as oral delivery systems of phenolic compounds: Overcoming pharmacokinetic limitations for nutraceutical applications

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Abstract

Drug delivery systems, accompanied by nanoparticle technology, have recently emerged as prominent solutions to improve the pharmacokinetic properties, namely bioavailability, of

therapeutic and nutraceutical agents. Solid lipid nanoparticles (SLNs) have received much attention from researchers due to their potential to protect or improve drug properties. SLNs have been reported to be an alternative system to traditional carriers, such as emulsions, liposomes and polymeric nanoparticles. Phenolic compounds are widespread in plant-derived foodstuffs and therefore abundant in our diet. Over the last decades, phenolic compounds have received considerable attention due to several health promoting properties, mostly related to their antioxidant activity, which can have important implications for health. However, most of these compounds have been associated with poor bioavailability being poorly absorbed, rapidly metabolized and eliminated, which compromises its biological and pharmacological benefits. This paper provides a systematic review of the use of SLNs as oral delivery systems of phenolic compounds, in order to overcome pharmacokinetic limitations of these compounds and improved nutraceutical potential. In vitro studies, as well as works describing topical and oral treatments will be revisited and discussed. The classification, synthesis and clinical application of these nanomaterials will be also considered in this review article.

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Keywords: Solid lipid nanoparticles, phenolic compounds, pharmacokinetics, oral absorption, bioavailability, nutraceutical potential,

1. Introduction

Solid lipid nanoparticles (SLNs) were introduced, for the first time, in the early 1990s, and are prepared from a lipid matrix, with final particle sizes ranging between 50 and 1000 nm (Müller et al., 2000). They were developed to overcome problems related with traditional unstable colloidal systems such as emulsions, lipospheres, lipossomes and polymeric particles. Emulsions are transparent solutions with larger quantity of surfactant containing micro or nano-droplets, with high size variability. These phenomena can lead to problems such as aggregation and flocculation of the droplets, which constrain their application in the final product. Lipospheres are small droplets, normally with sizes ranging between 400-4000 microns, used as matrix polymers, which may be obtained from animal, vegetable or synthetic sources. Other type of carriers - lipossomes - are spherical vesicles composed of an outer bilayer of amphipathic molecules, such as phospholipids with an aqueous compartment inside. Typically, they can be formulated from a variety of lipids and lipid mixtures with different compositions. Finally, polymeric nanoparticles are produced from biodegradable polymers and possess as main advantage the capacity to prolong the release of the incorporated drugs, and the disadvantage that some materials used to produce polymeric nanoparticles are cytotoxic. Hence, SLNs were proposed, in part, to overcome problems related with the aforementioned systems, but adequate and safe polymers must be selected.

The reduction of particle size and the use of nontoxic materials make SLNs important carriers, combining advantages such as the possibility of controlled drug release and drug targeting, excellent tolerability, capacity of incorporating hydrophilic and lipophilic drugs, increased physical drug stability, enhancement of bioavailability of the entrapped bioactive, which make

them one of the most currently used systems (Parhi and Suresh, 2010; Weiss et al., 2006; Severino et al., 2011). In addition, SLNs are more easily and cheaply manufactured than polymeric NPs and reveal facility of large-scale production and sterilization, which is suitable for industrial production.

The potential application of this type of nanoparticles for different purposes, such as in medicine, pharmaceutical industry, cosmetics, agriculture and other sectors, is already a reality and the applications are beginning to impact food-associated industries (Müller et al., 2000; Müller et al., 2002; Lai F et al., 2006; Weiss et al., 2008). In the field of food nanotechnology and considering the health promoting properties of phenolic compounds, over the last years many studies associated with the development of delivery systems of phenolic compounds have been published (Munin and Edwards-Lévy., 2011; Rein et al, 2013), especially to overcome the problem of oral absorption and bioavailability, allowing a greater nutraceutic effect associated with these compounds.

Identifying the bioavailability of phenolic compounds is essential when evaluating their potential health benefits as well as their toxicity. Bioavailability is usually defined as the relative amount of an ingested nutrient or compound that reaches the systemic circulation and the specific sites where it can exert its biological action (Porrini and Riso, 2008). The bioavailability and pharmacokinetics of orally ingested phenolic compounds faces some challenges including the specific physical chemical properties, transporters, molecular structures, and metabolizing enzymes. However, unraveling the bioavailability of phenolic compounds incorporated in functional foods is even more challenging than with drugs since many other factors such as bio-accessibility, food matrix effect and the gut microbiota can affect bioactive food compounds

during digestion. Based on this, strategies to improve bioavailability of the polyphenols need to be properly defined and whether these methods translate into increased biological activity should be confirmed.

This review article surveys recent advances in the application of SLNs loaded with phenolic compounds, in order to modify the pharmacokinetic profile and improve bioavailability and nutraceutical potential. In vitro studies, as well as topical and oral treatments previously reported will be revisited. The classification, synthesis and clinical application of these nanomaterials will be also discussed in this review article

2. Methods of SLNs production and characterization

A wide variety of SLNs have been developed, and it has been determined that in their formulation, lipid, emulsifier and water are needed as essential excipients. The lipids normally have a melting point above room and body temperature and by definition can be triglycerides, mono, di and triglycerides mixtures, waxes, hard fats and other types of lipids, as can be seen in Table 1. The emulsifiers, used to stabilize the lipid dispersion, are commonly types of poloxamer and polysorbate, but also lecithin, tyloxapol, sodium cholate and sodium glycocholate, taurodeoxychocolic acid sodium, butanol and butyric acid, cetylpyridinium chloride, sodium dodecyl sulphate, sodium oleate, polyvinyl alcohol and cremophor EL (Severino et al., 2011; Müller et al., 2000).

Several methods are available to prepare SLNs, such as high pressure homogenization technique (hot and cold), microemulsion, solvent emulsion by evaporation or by diffusion, melt dispersion, double emulsion, high speed stirring and ultrasonication techniques. Several novel techniques are

also used such as membrane contactor, solvent injection, multiple emulsion and supercritical fluid technology (Parhi and Suresh, 2010). All of these products and procedures can combine encapsulation of different functional ingredients (Table 2).

The SLNs-based systems aggregate several advantages, namely the improvement in design and function of some materials or systems at a nanoscale level, the possibility of improving the stability of the incorporated compounds and their interaction with the environment in which the system/material is included as well as enabling a modulated release action. Among the array of characteristics that can be improved, *e.g.* better water solubility, thermal stability, increased oral bioavailability of compounds (particularly lipophilic molecules, *e.g.* labile drug molecules can be protected from external environment during storage) and the digestive process protection (following oral administration), these systems may also improve the organoleptic and functional properties. Additionally, these SLNs-based systems include, in general, compounds that hold a Generally Recognized as Safe (GRAS) status for oral and topical administration (Severino et al., 2011). The disadvantages of this method, considering that the dispersions of SLNs are usually employed in matrices that have a high amount of water, include the fact that the loading capacity of SLNs is directly proportional to the crystalline structure of the solid lipid and the increase in particle size, flocculation, aggregation and compound release are all phenomena that can occur during storage time (Das and Chaudhury, 2010).

Although SLNs are usually produced via the homogeneous matrix model (Type I SLNs), the preparation methods may influence the structure of the final products. There are also core-shell type SLNs with drug-enriched shell (Type II SLNs) and with drug-enriched core (Type III SLNs) (Müller et al., 2000). The Type I SLNs are produced by the cold homogenization technique and

without use of surfactants or less drug-solubilizing surfactant. However, the hot homogenization method sometimes produce Type II SLNs, when high concentration of surfactants are used, which can lead to burst release of the drugs and should be avoided (Lukowski and Werner, 1998). The Type I SLNs are produced in case the drug precipitates first, before the lipid recrystallizes, which is useful to achieve prolonged release of the incorporated drugs (Souto et al., 2004; Westesen et al., 1997). Therefore, optimization of the preparation techniques should aim at production of type I or III rather than type II SLNs. To establish an adequate characterization of SLNs there is a need for the quality control of the product. Characterization of SLNs is a serious challenge due to the small size of the particles and the complexity of the system. Some parameters have to be considered, which have direct impact on the stability, release kinetics and *in vivo* behaviors, such as particle size, zeta potential, degree of crystallinity, co-existence of additional colloidal structures and dynamic phenomena (Müller et al., 2000). Photon correlation spectroscopy and laser diffraction are the most powerful techniques for routine measurements of particle size. Photon correlation spectroscopy can cover a size range from a few nanometers to about 3 μm. Electron microscopy and atomic force microscopy (AFM) provides additional information on the morphology of SLNs (zurMuhlen et al., 1996). Zeta potential measurements allow predictions of the storage stability of colloidal dispersions. Generally, dispersions with a zeta potential higher than ±30 mV are considered as physically stable due to electrostatic repulsion (Campos et al., 2014). Furthermore, differential scanning calorimetry and X-ray powder diffraction are widely used to investigate the solid state of the lipid as well as the incorporated compounds (Bunjes et al., 1996). The nuclear magnetic

resonance and electron paramagnetic resonance are powerful tools to investigate the dynamic phenomena and the characteristics of nano-compartments in colloidal lipid dispersions.

3. Phenolic compounds – benefits and limitations for nutraceutical use

Phenolics are a class of diverse natural organic and chemical compounds, which include several hundred molecules, found in both edible and inedible plants, particularly in their fruits and leaves (Kähkönen et al., 1999). These compounds are usually secondary plant metabolites and responsible for some of the major functional properties and main organoleptic characteristics (*e.g.* colour and flavour) of foods and beverages, namely tea, wine and fruits (Dimitrios, 2006; Kaur and Kapoor, 2001).

In terms of structure, phenolic molecules are composed by an aromatic ring with one, or more, hydroxyl groups attached. Depending on the amount of carbons present in their structure, they can be classified as phenolic acids, polyphenolic compounds (phenolics that contain more than one phenolic hydroxyl group attached to one or more benzene rings), flavonoids, stillbenes and lignans, among others (Tabasco et al., 2011; Vermerris and Nicholson, 2008).

In the last decades, these molecules have shown a considerable potential towards the protection from and/or amelioration of several diseases (Berardini et al., 2005), given the amount of health promoting properties that have been ascribed to the phenolic compounds (Figure 1). Examples of their beneficial impact on human health can be associated with their antioxidant, anti-inflammatory, anti-microbial, anti-mutagenic and anti-carcinogenic properties, as well as capacity to stimulate the digestive process (Aaby et al., 2004). Their properties are one of the primary reasons for the increased interest of the food industries in this particular class of

compounds. From a technological point of view they are able to protect the biologically important cellular components, such as DNA, proteins, and membrane lipids, from reactive oxygen species (ROS) attacks and thereby improve the quality and nutritional value of products therewith (Wojdylo et al., 2007).

The human body produces ROS by many enzymatic systems through oxygen consumption. In small amounts these species can be beneficial as signal transducers and/or growth regulators, but when present in larger amounts, during oxidative stress, they can be implicated in several diseases. Being phenolic compounds strong antioxidants, their exogenous consumption is required, because these compounds disrupt the chain of oxidation reactions acting as a neutralizer, balancing the percentage of ROS in human body (Ma et al., 2011; Lu et al., 2012).

The perspective of using phenolic compounds in the food industry has increased, but the incorporation of these compounds has been in some cases challenging. One of the major drawbacks for industrial application is the fact that they are very reactive and may interact with either the matrix or the environment components, thus losing their antioxidant activity (Manach et al., 2004; Munin and Edwards-Lévy, 2011). Specifically, their incorporation into foods may cause quality defects such as adstringent taste and increased haze in beverages and act as substrates for browning reactions (Lesschaeve and Noble, 2005) resulting in undesirable color changes and flavors in food products; furthermore, complexation with food proteins may jeopardize nutritional value, since proteins become unavailable for absorption and digestion. Moreover, their stability can be negatively affected by degradation and/or deterioration by food processing operations and storage (*e.g.* heating, acidification, light and oxygen) or in the gastrointestinal tract (acidic pH, enzymes, presence of other nutrients) (Munin and Edwards-

Lévy, 2011). Nanoencapsulation of bioactive molecules within appropriately structured carriers may overcome these problems without adverse effect on sensory characteristics and appearance of final product; indeed, this is one of the major challenges in this area of knowledge.

Figure 1 schematically presents the benefits and limitations for the use of phenolic compounds in nutraceutical applications, and the advantages of use SLNs to overcome some of those difficulties, which will be further discussed.

4. Nanoparticles with phenolic compounds

There are several types of phenolic compounds loaded nanoparticles. Some of them include pure phenolic compounds, fruits extracts or tea polyphenols for antimicrobial, antioxidant and anticancer properties, as shown in Table 3.

Tea polyphenol and vitamin E loaded liposomes were investigated in order to offer a new approach to entrap an aqueous soluble drug and an insoluble drug together (Fang et al., 2005; Ma et al. 2009) for local delivery, including skin and tumor deposition. Later nano-tea liposomes were formulated using lecicthin and cholesterol by dispersion method and their characterization showed that they were stable and suitable for widespread applications (Lu et al., 2011).

Silver nanoparticles synthesized through bio-green method have been reported to have biomedical applications to control pathogenic microbes as it is cost effective compared to commonly used physical and chemical methods. In the study of Reddy et al. (2014), silver nanoparticles were synthesized using aqueous *Piper longum* fruit extract and confirmed by UV-visible spectroscopy. Mucoadhesive polymeric nanoparticles as a delivery system of natural products (red grape seed extract) were also developed, aiming to protect from oxidative stress the

bone marrow-derived endothelial progenitor cells (EPCs), which contribute to neo-vascularisation and re-endothelialisation as part of the process of vascular repair (Felice et al., 2013).

Chitosan nanoparticles (CS-NPs) as carriers of tea polyphenols were prepared with antitumor activity towards HepG2 cancer cells (Liang et al., 2011). This type of nanoparticles is capable of enhancing epigallocatechin gallate (EGCG) bioavailability present in tea extract (Hu et al., 2012; Dube et al., 2010). Dube et al. (2011) measured the plasma concentrations of EGCG in mice after oral administration of either free EGCG or EGCG-encapsulated CS-NPs; when compared to free EGCG, EGCG-loaded CS-NPs increased plasma EGCG concentrations by a factor of 1.5.

Nano-scale emulsion systems also enhanced the oral bioavailability of lipophilic compounds through improving their aqueous solubility, increasing passive diffusion rate, and facilitating direct uptake by intestinal lymphatic system. The bioavailability studies of lipophilic nutraceuticals, such as puerarin found in roots of *Pueraria lobaota* (Yu et al., 2011), curcumin from *Curcuma longa L.*(Yu and Huang, 2012), and resveratrol, extracted from grape skin (Sessa et al., 2014), in nanoemulsion systems showed significant improvement in bioavailability when compared to non-emulsion based oral formulations. Iron-based nanoparticles were synthesized using oolong tea extracts for environmental remediation removing 75.5% of malachite green (50 mg/L) (Huang et al., 2014).

EGCG, tannic acid, curcumin and theaflavin were encased into gelatin-based 200 nm nanoparticles consisting of a soft gel-like interior with or without a surrounding Layer-by-Layer shell of polyelectrolytes (polystyrene sulfonate/polyallylamine hydrochloride, polyglutamic acid/poly-L-lysine, dextran sulfate/protamine sulfate, carboxymethyl cellulose/gelatin, type A)

assembled using the layer-by-layer technique. Nanoparticle-encapsulated EGCG retained its biological activity and blocked hepatocyte growth factor (HGF)-induced intracellular signaling in the breast cancer cell line MBA-MD-231 as potently as free EGCG (Shutava et al., 2009).

The synthesis and investigation of the protective effect of poly(lactide-co-glycolide) nanoparticles (PLGA-NPs) on polyphenols from black tea theaflavin (TF) and green tea EGCG against chemically induced DNA damage was performed by Srivastava et al. (2013). This study showed that PLGA-loaded tea polyphenols have approximately 30-fold dose-advantage over bulk tea polyphenols. Additionally, TF- or EGCG-loaded PLGA-NPs showed significant potential for induction of DNA repair genes and suppression of DNA damage responsive genes as compared with respective bulk TF or EGCG doses. Taken together, TF- or EGCG-loaded PLGA-NPs showed a superior ability to prevent DMBA-induced DNA damage at much lower concentrations, thus opening a new dimension in chemoprevention research. Encapsulated curcumin in PLGA-NPs was also developed by Yallapu et al. (2010) with the aim of using this formulation for improvement of therapeutic effects in metastatic cancer cells. The nanoparticle formulation showed a greater inhibitory effect on the growth of metastatic cancer cells compared to free curcumin.

Tan et al. (2012) synthesized quercetin-loaded nanomicelles and found that they were stable in gastric and intestinal fluids and had no toxic effects on Caco-2 cells. Both free quercetin and quercetin-loaded nanomicelles decreased the viability of A549 lung cancer cells *in vitro*, but 100 μM of free and nanoquercetin decreased the cell viability to 60% and 100%, respectively. In addition, Wang et al. (2012a) demonstrated that quercetin nanoliposomes decreased the viability of C6 glioma cells and induced necrotic death of those cells. Frozza et al. (2010) encapsulated

resveratrol into lipid-core nanoparticles and showed that this nanoresveratrol has a potential in improving resveratrol's preventive effect on Alzheimer's disease, which is also demonstrated in a study using the resveratrol-loaded polymeric micelles (Lu et al., 2009) (Table 3).

5. Solid lipid nanoparticles with phenolic compounds

Several research works were performed regarding the loading of phenolic compounds or phenolic-rich extracts in SLNs (Table 4). The solid lipid matrix has been shown to protect the chemically labile compounds such as phenolic compounds from degradation (Trombino et al., 2009). Recent advances on their formulation in nanoparticulate systems for targeted therapy and increased bioavailability was reviewed by Santos et al. (2013). Most of them were used in *in vitro* experiments and *in vivo* studies mainly in skin diseases formulations and topical administration. Nevertheless, the development of drug delivery systems for oral administrations is also already established.

5.1. *In vitro* studies

A novel drug delivery system consisting of benzoic acid, 2-hydroxy-, 2-D-ribofuranosylhydrazide (BHR)-loaded solid lipid nanoparticles (BHR-SLNs) was prepared using the emulsification-evaporation technique. The treatment of 293T and Hela cells with BHR-SLNs demonstrated that BHR-SLNs were less toxic than normal cells, while more effective in antitumor potency compared with the BHR drug alone. These results showed that BHR-SLNs could be considered as a promising antitumor drug system for a range of new therapeutic applications (Wang et al., 2012b).

On the other hand, some applications on neurological diseases have been proposed. Oxidative stress and dysfunctional mitochondria are among the earliest events in Alzheimer's disease (AD), triggering neurodegeneration. The use of natural antioxidants could be a neuroprotective strategy for blocking cell death. Here, the antioxidant action of ferulic acid on different paths leading to degeneration of recombinant beta-amyloid peptide (rAbeta42) treated cells was investigated. Ferulic acid treatment, in particular if loaded into SLNs, decreased ROS generation, restored mitochondrial membrane potential (Deltapsi(m)) and reduced cytochrome c release and intrinsic pathway apoptosis activation. Further, ferulic acid modulated the expression of peroxiredoxin, an anti-oxidative protein, and attenuated phosphorylation of ERK1/2 activated by Abeta oligomers (Picone et al., 2009).

Stearic acid- and stearyl ferulate-based SLNs containing trans-ferulic acid (SLN-FA and SLN-SF-FA, respectively) were produced using the hot homogenization method, with polysorbate 20 as surfactant. These were tested using rat brain microssomes, for *in vitro* evaluation of the antioxidant activity against three initiators of lipid peroxidation (AAPH, NADPH/ADP-Fe^{3+} and SIN-1), which in turn generated the peroxyl and perferryl radicals as well as peroxynitrite, respectively. SLN-SF-FA displayed greater efficacy (EC_{50}) and potency (maximal activity) against AAPH- and NADPH/ADP-Fe^{3+}-induced lipid peroxidation. These results suggested that these formulations could facilitate the uptake of ferulic acid by the cells because of their lipophilic structure, thus increasing ferulic acid bioavailability. Furthermore, stearyl ferulate-based nanoparticles could prevent the degradation of ferulic acid entrapped on their structure, making ferulic acid almost entirely available to disclose its antioxidant power once released (Trombino et al., 2013).

5.2. Topical treatment

The success of SLNs for topical administration gave new perspectives to the use of cosmetic ingredients that suffer chemical instability in traditional formulations (Kaur et al., 2007). The occlusive effect of SLNs leads to an increase in skin hydration and, thus, to wrinkle smoothing, enhancing the penetration of compounds in specific skin layers, which is a fundamental requirement for the efficacy of cosmetic treatments (Uner, 2006).

Plianbanchang et al. (2007) studied the efficacy and safety of curcuminoids-loaded SLNs facial cream as an antiaging agent. Furthermore, the light and oxygen sensitivity of curcuminoids was strongly reduced by incorporating these compounds into SLNs. This study with healthy volunteers revealed the improved efficiency of a topical application cream containing curcuminoid loaded SLNs, characterized by improved skin wrinkles, hydration, melanin content, biological elasticity, and viscoelasticity, over that containing free curcuminoids.

Sesamol, a natural phenolic antioxidant, present in sesame seeds has been shown a potential ROS scavenging ability, which can be useful in combating skin cancers (Ramachandran et al., 2011); however, its physicochemical characteristic limits the local actions of sesamol in the skin tissue. Thus, sesamol-loaded solid lipid nanoparticles (S-SLNs) and its subsequent incorporation into a cream base (to easy application) were developed to improve the performance of sesamol in terms of permeability, local bioavailability in skin tissue and prolonged effect. The authors confirmed by in-vivo skin retention and ex-vivo skin permeation studies that incorporation of S-SLN into cream base significantly improved retention in the skin with minimal flux across skin.

Furthermore, S-SLNs treatment showed ability to induce the normalization of skin cancers post their induction (Geetha et al., 2014).

A recent *in vitro* study performed by Han and colleagues (2014) suggested quercetin-loaded solid lipid nanoparticles, prepared with a surfactant content of 2%, exhibited high skin permeability and could be used as useful skin delivery system for transdermal delivery of hydrophobic antioxidants.

Besides phenolic compounds, SLNs have also been employed in other relevant antioxidants, improving their stability and allowing application, for example on skin carcinogenesis originated by DNA damage from UVA exposure. Antioxidants are usually employed as protective agents to avoid this problem; in particular, both β-carotene and α-tocopherol can protect the skin against UVA-induced damage. It is well known that the photochemical instability of these compounds has been a limiting factor for their applications to protect skin. Stearyl ferulate-based solid lipid nanoparticles (SF-SLNs), as carriers for β-carotene and α-tocopherol, were formulated to improve the stability of these compounds. Those findings highlighted how SF-SLNs represent a suitable carrier for β-carotene and α-tocopherol stabilizing and protecting them from degradation. A dermatological formulation in order to prevent skin damage is, therefore, suggested (Trombino et al., 2009).

Vitamin E has several isomers, including α-tocopherol, which is the most abundant form in nature, and the only form of vitamine E that is actively maintained in the human body. Vitamin E is used as an antioxidant and skin care substance in dermopharmaceutical and cosmetic products. Pure tocopherol was found to show the greatest UV-blocking capacity; however, stability was decreased to the greatest extent as well (McVean and Liebler, 1997). Hence, the

SLN loaded with chemical sunscreen tocopherol acetate was developed to prevent chemical degradation and increases the UV-blocking capacity and consequently, leading to an improved sunscreen and skin care formulation (Wissing and Müller, 2001).

Alpha-lipoic acid (LA) was also formulated in the form of SLNs in an effort to develop a water-soluble formulation for topical administration and characterized in terms of physical and biological properties, for aqueous topical administration of LA (Ruktanonchai et al., 2009).

5.3 Oral treatment

Campos et al. (2014) performed a recent work based on development of SLNs produced with rosmarinic acid and their herbal extracts for oral administration. The process of production of these nanoparticles was optimized varying the concentrations of lipid – witepsol wax, and surfactant – tween 80, and using the hot homogenization technique. High efficiencies of association between rosmarinic acid and the lipid were obtained, as well as highly stable nanoparticles during the storage time period of 28 days.

A study on curcumin loaded SLNs was performed by Wang et al. (2012c) with the objective of using them in formulations for improvement of the therapeutic efficacy of curcumin in the treatment of asthma. They found that nanocurcumin dramatically increased curcumin concentrations in lung and doubled the inhibitory effect of the free compound on the inflammatory responses in the lung, thus implying its application in asthma therapy. Recently, in a study conducted by Ramalingam and Ko (2014) the surface of the SLNs were capped with chitosan and N-trimethyl chitosan (TMC, a quaternized chitosan derivative), for the enhancement of the oral bioavailability of curcumin. This study showed that N-trimethyl

chitosan coated solid lipid nanoparticles (TMC-SLCNS), exhibited prolonged stability. This improvement resulted from the TMC-mediated protection of SLNs in acidic conditions, which prevented the burst release of the drug in the gastric environment, suggesting that the TMC-SLNCs can be used as a nanocarrier system to improve the oral bioavailability and brain distribution of the curcumin.

Resveratrol is a polyphenol that can be found in considerable amounts in grapes and red wines. Interest in this polyphenol has increased due to its pharmacological cardio- and neuroprotective, chemopreventive, and anti-aging effects, among others. The encapsulation was suggested, owing to its pharmacokinetic properties, such as poor bioavailability, low water solubility, and chemical instability. The development of lipid nanodelivery systems (NLC and SLN) to overcome these problems was made (Neves et al., 2013). To increase the resveratrol oral bioavailability for further use in medicines, supplements, and nutraceuticals, SLNs were formulated conferring protection to the incorporated resveratrol and allowing a controlled release after uptake (Pandita et al., 2014).

6. Oral route and pharmacokinetic behavior of phenolic compound SLNs

As it can be seen, SLNs can be administrated through oral, parenteral, dermal, rectal, nasal, ocular and pulmonary routes. Oral delivery of drugs incorporated in SLNs has gained considerable interest over the last two decades. It is the most preferable route for the application of SLNs and continues to be a challenge, as well as the most attractive way to administer drugs due to its unquestionable commercial potential and its plainness administration and patient compliance (Gamboa and Leong, 2013).

SLNs may be either administered as an aqueous dispersion or after incorporation into a traditional dosage form (tablets, pellets, capsules or powders in sachets). The aqueous SLNs dispersion may be used as the granulation fluid in the granulation process or can be spray-dried into a powder and mixed with the necessary excipients before compression into tablets. SLNs dispersion can also be used as wetting agent in the extrusion process for the production of *pellets* (Waghmare et al., 2012). Alternatively, SLN powders can be filled in hard gelatin capsules or incorporated in liquid PEG and filled into soft gelatin capsules. The spray-dried or lyophilized powders can even be filled into sachets. The physical characteristics of the resultant SLN powder like flow property, compressibility, bulk density, waxy nature and strength to withstand the compression force and temperature, need to be carefully addressed before production of the final dosage form.

Advantages of the use of SLNs for oral and peroral administration are the possibility of drug protection from hydrolysis, increase of drug bioavailability and improved therapeutic performance. Prolonged plasma levels have also been postulated due to a controlled, optimized release in combination with general adhesive properties of small particles (Montisci et al., 2001). The advantage of these colloidal drug carriers is that they are generally linked to their size in the submicron range. Therefore, the preservation of particle size of colloidal carrier systems after peroral administration is a crucial point. It is possible to produce stable SLN dispersions by optimizing the surfactant/mixture for each lipid *in vitro* (Zimmermann and Müller, 2001).

The *in vivo* biodistribution of the SLNs is dependent on the administration route and interactions of SLN with biological surrounding which, in general, include two types of process: distribution process (adsorption of biological material on the particle surface and desorption of SLN

components into the biological surrounding) and enzymatic process (lipid degradation by lipases and esterases).

Physiologically related lipids or waxes generally constitute the SLNs. Therefore, the *in vivo* fate of the carrier, to a large extent, occurs through the pathways of transportation and metabolism present. The gastric environment (ionic strength, low pH) may destabilize the SLN and potentially lead to aggregation. Lipases, the enzymes present in various organs and tissues of the body are the most responsible for SLNs degradation. Lipases split the ester linkage and form partial glycerides or glycerol and free fatty acids. Activation by an oil/water interface, which opens the catalytic centre, is a pre-requisite for lipases to act (Scow and Olivecrona, 1977; Borgstrom, 1980). SLNs show *in vitro*, different degradation rates, by the lipolytic enzyme pancreatin lipase as a function of their composition (lipid matrix, stabilizing surfactant) and it has been demonstrated that the longer the fatty acid chains of the acylglycerols are, the slower is their degradation (Olbrich and Müller, 1999).

In general, oral administration is the most practical and acceptable route for long-term administration of phytochemicals and dietary supplements. Noninvasive monitoring is naturally preferred, but options as well as details of extracted information would be limited. Appropriately designed *in vivo* studies of formulations, usually performed in the early phases of drug development, can provide important information about the impact of the excipients on the overall bioavailability and pharmacokinetic profile of the drug. Together with information from *in vitro* studies, these investigations can be a primary basis for labeling statements (e.g. to be taken with/ without food) and can often help avoid the need for further investigations.

Pharmacokinetic studies conducted by Liu et al. (2006) showed a significant improvement in curcumin bioavailability due to curcumin-phospholipid complex formation. Curcumin is a hydrophobic polyphenol with anti-inflammatory, antiangiogenic and antitumorogenic properties. In this study, curcumin (100 mg/kg) and curcumin-phospholipid complex (corresponding to 100 mg/kg of curcumin) were administered orally to Sprague-Dawley male rats. Curcumin-phospholipid complex showed a maximum plasma curcumin level of 600 ng/mL 2.33 h after oral administration as opposed to that of free curcumin having maximum plasma concentration of 267 ng/mL after 1.62 h of oral dosing. About a 1.5-fold increase in curcumin half-life in rats was found in this study for the curcumin phospholipid complex over free curcumin, together with significantly increase circulating levels of presumably active curcumin in rats. Moreover, the efficacy of curcumin as a chemopreventive agent was augmented when incorporated into nanocapsule system developed by Ghosh et al. (2012). Nanocapsulated curcumin reduced oxidative stress, suppressed tumor cell proliferation, and reduced patho-morphological structures in a diethylnitrosamine induced rat hepatocellular carcinoma model.

Li et al. (2009) reported that the quercetin plasma concentrations were significantly higher for rats treated with QT-SLNs suspension than for those treated with quercetin suspension. The Cmax value of quercetin in SLNs (12.22 μg/mL) was higher than that obtained with quercetin in CMC-Na suspension (5.90 μg/mL). Forty-eight hours after oral administration of QT-SLNs suspension (50 mg/kg of quercetin), the quercetin plasma concentration was still more than 2 μg/mL, whereas it was undetectable at 16 h for quercetin suspension. The area under curve − AUC (0→48h) value of quercetin after oral administration of quercetin in suspension was 56.73 μg/mL.h, and 324.18 μg/mL.h for QT-SLNs suspension, which was 5.71 times greater than that

of the quercetin suspension. These results showed that incorporation into SLNs resulted in increased absorption of quercetin by oral administration. In another study, Maiti et al. (2005) applied a phospholipid complexation method as quercetin delivery system to enhance the inhibition of CCl_4 induced acute liver injury in rats via improved free radical scavenging activity. Lou et al. (2011) investigated the pharmacokinetics and the bioavailability in rats after intragastric administration of puerarin or puerarin-solid lipid nanoparticles (Pue-SLNs). It was shown that plasma concentration of puerarin suspension reached a peak of 0.16 μg/ ml at 110 min after oral dosing (20 mg/ kg), whereas after intake of Pue-SLNs, a peak of 0.33 μg/ml occurred at earlier in time, 40 min. In this study, the ratios of Cmax in the brain and heart after the administration with Pue-SLNs and the puerarin suspension were 2.52 and 1.28, respectively. Orally administered Pue-SLNs were rapidly absorbed, as evidenced by a shorter Tmax for Pue-SLNs than for puerarin suspension and the tissue concentrations of puerarin increased after a single-dose oral administrationof Pue-SLNs, especially in its target organs, the heart and brain. These data collectively support that SLNs are a promising delivery system for the enhancement of oral absorption of puerarin, a poorly water-soluble drug.

Thus, the currently available evidences have proven that bioactive compounds delivery systems are effective in enhancing oral efficacies of nutraceuticals to provide physiological and therapeutic benefits.

6.1. Absorption and oral bioavailability of phenolic compound loaded SLNs

Nanometric size delivery systems can contribute to increase the bioavailability of bioactive compounds through their protection during the digestive processes, as well as their improved uptake in the gastrointestinal tract (GIT) and enhanced transport to the target sites.

Absorption of nanoparticles occurs through mucosa of the intestine by several mechanisms, namely through the Peyer's patches, by intracellular uptake or by the intercellular/paracellular pathway. The absorption behavior is reported to enable bypass of gastric and intestinal degradation of the encapsulated drug/bioactive compound and their possible uptake and transport of integral form through intestinal mucosa (Chakraborty et al., 2009).

The main reason for many drugs which exhibit poor oral bioavailability is due to their extensive first-pass metabolism. In order to overcome this problem, intestinal lymphatic transport of drugs can be exploited. Transport of such drugs or carriers through the intestinal lymphatic vessels via thoracic lymph duct to systemic circulation joining at the junction of the jugular and left subclavian vein avoids pre-systemic hepatic metabolism and, as a result, enhances the amount of orally administered drugs reaching into systemic circulation and viscera. Studies have also been reported that SLNs may exhibit bio-adhesion to the GIT wall, increasing their residence time in GIT, enhancing bioavailability and reducing or minimizing erratic absorption (Ponchel et al., 1997; Müller et al., 2000).

The extent of particles absorption in the GIT is affected by size, surface chemistry and charge, length of administration, and dose (Harde et al., 2011). In terms of size, particle uptake diminishes for larger particles (Jani et al., 1990). In fact, smaller particles have been reported to show greater absorption as compared to larger particles independent of animal model; larger particles are retained for longer duration in the Peyer's patches as compared to smaller particles,

which exhibit very high uptake and are easily released from Peyer's patches thereby facilitating their transport to the lymphatic system (Bargoni et al., 1998). Desai et al. (1996) also showed that bio-degradable nanoparticles of 100 nm size had 15- to 250-fold higher uptake efficiency as compared to larger sized microparticles (> 500 nm). Furthermore, particles >500 nm have been reported to show erratic delivery through the abdominal cavity and restricted targeting. Thus, like other nanoparticulate system, submicron SLNs are absorbed to significantly higher extent than larger particles. Despite these discussions, no data has been published so far concerning the stability of SLNs in the GIT.

Before a drug is able to pass through a physiological barrier it must be in a dissolved state (Ruckenstein and Shulgin, 2005). Important parameters that affect drug absorption and thus its bioavailability through the GIT include: (i) solubility and ionization state of drug in the lipids, (ii) aqueous solubility of drug required to provide an appropriate concentration gradient, (iii) oral dosage form, i.e. the drug release profile and dissolution rate, (iv) GIT motility, (v) blood flow and eventual pathological changes, (vi) gut microbiota, which may metabolize some drugs, and (vii) presence of food and/or other medicines in the GIT.

Recent bioavailability experimental research on SLNs showed positive results. Solid lipid nanoparticles have been used as drug delivery systems for enhancing the bioavailability of phytochemical compounds such as quercetin, curcumin, resveratrol and puerarin as previously mentioned (Table 5).

Li et al. (2009) showed enhanced oral absorption of drug-loaded SLNs through different segments of the GIT with different patterns and extents of absorption. To confirm this mechanistic absorption of SLNs, quercetin-loaded SLNs (QT-SLNs) were administered by oral

route in Wistar rats and their pattern of absorption observed in both stomach and intestine. The results indicated that QT-SLNs could be absorbed in all GIT segments with different percentages and patterns of absorption. The absorption of SLNs was only 6% from stomach while 82% from intestine and colon region. It was clearly shown that a large surface area for adhesion and the presence of M cells in Peyer's patches were preferable mechanism for oral absorption of SLNs in intestine and colon. Pharmacokinetic results, as already mentioned in this review, further confirmed improved bioavailability by more than 5-fold using QT-SLNs as compared to quercetin suspension.

Curcumin has poor aqueous solubility, has low bioavailability and is quickly metabolized by hepatic enzymes in humans and research animals. After encapsulating curcumin into SLNs, nanoemulsions and PLGA nanoparticles, the oral bioavailability can be enhanced more than 2-fold (Xie et al., 2011; Kakkar et al., 2011). Another study revealed that nanoparticle encapsulation improves the oral bioavailability of curcumin by at least 9-fold when compared to curcumin administered with piperine as an absorption enhancer (Shaikh et al., 2009). In mice, curcumin nanoparticles were more bioavailable and had a longer half-life than free curcumin (Anand et al., 2007).

Neves et al. (2013) performed an *in vitro* resveratrol release study simulating the gastrointestinal transit of the resveratrol-loaded lipid nanoparticles. These authors showed that the resveratrol remained mostly associated to the lipid nanoparticles after their incubation in digestive fluids suggesting that a nanodelivery system can be suitable for oral administration, conferring protection to the incorporated resveratrol and allowing controlled release after uptake. Frozza et al. (2010) encapsulated resveratrol (5 mg/kg body weight) into lipid-core nanoparticles and

treated orally (daily, for 14 days) male Wistar rats with either free or nanoresveratrol. Compared to free resveratrol, nanoresveratrol significantly increased the rat tissue (kidney, brain and liver, but blood was not measured) resveratrol concentrations by more than 2-fold. In addition, resveratrol-loaded lipid-core nanoparticles had higher gastrointestinal safety than free resveratrol.

Puerarin is a cardioprotective agent used in cerebro-vascular diseases, which is greatly restricted due to its poor solubility and short half life. Currently, no oral formulation of puerarin is available and frequent intravenous administration of high doses may lead to severe and acute side effects. However, as suggested above, Pue-loaded SLNs after single intragastric administration showed 3.1-fold increase in oral bioavailability. Further, high tissue distribution in the heart may also be correlated with the improved efficacy and reduced side effects associated with free puerarin (Lou et al., 2011).

To sum up, the evidences described above strongly suggest that SLNs can be extensively used as efficient carrier system for drugs, including for phenolic compounds, thus overcoming limitations related with poor oral bioavailability.

7. Conclusions

The incorporation of phenolic compounds in food and beverages can offer beneficial health effects related to the prevention of several diseases and the promotion of new food products in the market. Thus, the development of strategies to enhance the absorption and improve the bioavailability of phenolic compounds is extremely important in medicine and food industry applications.

Oral bioavailability is the commonly anticipated factor, which plays a critical role in determining the bio-efficacy of bioactive compounds ingested through oral route. Overall, the studies discussed in this review indicated that SLN delivery systems are effective means to enhance the oral bioavailability of phenolic compounds. However, the evidences on the improvement of their efficacies by delivery systems were mainly examined by acute or short-term animal models. Therefore, to maximize the potential of delivery systems, more *in vivo* pharmacokinetic studies and clinical trials are needed to confirm the usefulness of specific delivery systems to improve phenolic compounds bioavailability and efficacy.

The optimization of formulations of nanoencapsulated phenolic compounds and the improved knowledge on safety data are the next steps before oral delivery systems can be utilized for general consumers, thus benefiting from the wide range of beneficial properties in several areas, including health and food industry.

Acknowledgments

Partial funding for this research work was provided via project NANODAIRY (PTDC/AGR-ALI/117808/2010) and project PEst-OE/EQB/LA0016/2013, financed by FCT (Fundação para a Ciência e Tecnologia, Portugal). Author Ana Raquel Madureira acknowledges FCT for the post-doctoral scholarship SFRH/BPD/71391/2010.

Conflict of interest statement

The authors have declared no conflict of interest.

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Table 1. Lipid compounds and substances commonly used to produce SLNs.

Group of lipids	Examples of substances
Triglycerides	Trimyristin, tripalmitin and tristearin
Mono, di and triglycerides mixtures	Witepsol bases, glyceryl monostearate, behenate and palmitostearate
Waxes	Beeswax, carnauba wax and cetyl palmitate
Hard fats	Stearic, palmitic and behenic acids
Other lipids	Miglyol 812 and paraffin

Table 2. Type of products loaded by SLNs.

Type of products	Examples
Enzymes	Porcine pancreatic lipase and colipase
Fatty acids	Omega-3
Vitamins	Vitamins E and D_2
Antibiotics	Clotrimazole, cyclosporine and rifampicin
Other products	Tea polyphenols, insulin, ketoprofen and bovine serum albumin

Table 3. Examples of some types of nanoparticles formulations loading phenolic compounds or phenolic extracts and associated therapeutic application.

NPs Type	Incorporated Compound	Therapeutic application	Reference
Nanolipossomes	Tea polyphenols Quercetin	Cancer	Fang et al. (2005) Ma et al. (2009) Wang et al. (2012a)
Silver NPs	Piper Longum fruit extract	Pathogenic microbes	Reddy et al. (2014)
Muchoadhesive polymeric NPs	Red grape seed extract	Coronary artery disease	Felice et al. (2013)
Chitosan-NPs	Tea polyphenols EGCG	Cancer Bioavailability	Liang et al. (2011) Dube et al. (2011)
Nanoemulsion	Puerarin Curcumin Resveratrol	Bioavailability	Yu et al. (2011) Yu and Huang (2012) Sessa et al. (2014)
Iron-based NPs	Oolong tea extract	Environment Remediation	Huang et al. (2014)

Layer-by-Layer-Coated Gelatin NPS	EGCG Taninic acid Curcumin Theaflavin	Breast cancer	Shutava et al. (2009)
PLGA-NPs	Theaflavin (blak tea) EGCG (green tea)	DNA damage	Srivastava et al. (2013)
	Curcumin	Cancer	Yallapu et al. (2010)
Nanomicelles	Quercetin	Lung cancer	Tan et al. (2012)
Polymeric micelles	Resveratrol	Alzheimer's disease	Lu et al. (2009)
Lipid-core NPs	Resveratrol	Alzheimer's disease	Frozza et al. (2012)

NPS, nanoparticules; PLGA, poly(lactide-co-glycolide); EGCG, epigallocatechin gallate.

Table 4. Examples of phenolic compounds and other bioactive compounds incorporated into SLNs.

Incorporated Compound	Method used	Application	Reference
Benzoic acid	Emulsification-evaporation technique	Cancer	Wang et al.(2012b)
Ferulic acid	Hot homogenization	Bioavailability	Trombino et al. (2013)
	Microemulsion technique	Neurological disease	Picone et al. (2009)
Curcumin	Solvent injection method	Respiratory disease	Wang et al. (2012c)
	High-shear homogenization, ultra-sonication technique	Oral bioavailability	Ramalingam et al. (2014)
Curcuminoids extract	Microemulsion technique	Antiaging agent	Plianbanchang et al. (2007)
Sesamol	Microemulsion technique	Skin cancer	Geetha et al. (2014)
Quercetin	Hot homogenization, ultrasonification method.	Skin permeability	Han et al. (2014)
Resveratrol	Hot homogenization	Oral bioavailability	Neves et al. 2013

	Solvent diffusion–solvent evaporation method		Pandita et al. (2014)
β-carotene, α-tocopherol	Microemulsion technique	Skin cancer	Trombino et al. (2009)
Alpha-lipoic acid	Hot homogenization	Antioxidant for Topical administration	Ruktanonchai et al. (2009)
Tocopherol acetate	High-pressure homogenization	Skin care formulation	Wissing and Müller (2001)

Table 5. Delivery systems studied to improve the oral bioavailability of polyphenolic compounds.

Study Application	Drug	NPs Type	Experimental Model/ Dose/ route of administration	Principal Notes	Reference
Bioavailability	Quercetin	SLNs (Glyceryl monostearate; Tween-80, and PEG 400, Soya Lecithin)	• Wistar rats • QT-SLNs suspension at a quercetin dose of 50 mg/kg • Intragastric route • *In situ* and *in vitro* study	• ↑ bioavailability • Prolonged Tmax and MRT • ↑ sustained release and blood QT concentrations	Li et al. (2009)
Bioavailability	Curcumin	Compritol 888, Polysorbate 80, soya lecithin, Tween 80	• Male Wistar rats • Dose: 1, 12.5, 25 and 50 mg/kg of nanocurcumin, or 50 mg/kg of free curcumin • Oral administration	• ↑ oral bioavailability • ↑ stability and sustained release	Kakkar et al. (2011)

Bioavailability	Resveratrol	Cetyl palmitate, polysorbate 60	• In vitro release and stability study • Dose: 0, 2, 5, 10, and 15 mg of resveratrol	• ↑ stability and sustained release • ↑ oral bioavailability	Neves et al. (2013)
Cardio-cerebrovascular disease	Puerarin	SLNs (Monostearin; Poloxamer 188, Soya Lecithin)	• Sprague-dawley rats • Pue-SLNs and puerarin free • Single intragastric dose:20mg/kg • Study of excretion of drug:1 week –same dosing	• ↑ Bioavailability • ↑ Tissue concentrations • ↑ absorption of drug	Luo et al. (2011)

NPs, Nanoparticles; SLNs, Solid lipid nanoparticles; PEG, polyethylene glycol; QT, Quercetin; MRT, mean residence time; ↑, increase/increment.

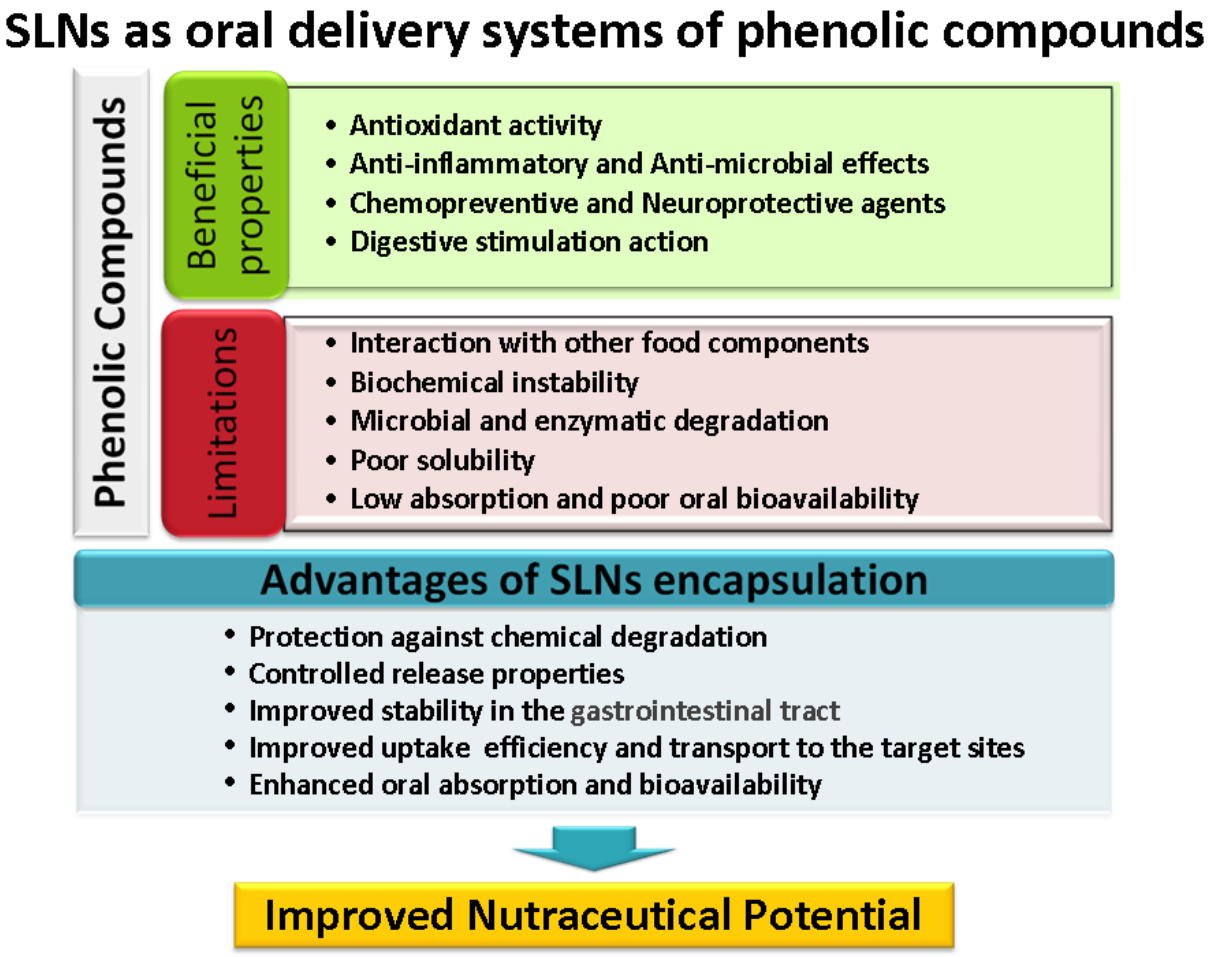

Fig. 1. Solid lipid nanoparticles as oral delivery systems of phenolic compounds: potential beneficial properties, namely in health and food industry applications, main difficulties/limitations for its complete use, and advantages of encapsulation in SLNs.