ELSEVIER

Trends in Food Science & Technology 23 (2012) 13–27

TRENDS IN FOOD SCIENCE & TECHNOLOGY

Review

Nanoencapsulation of food ingredients using lipid based delivery systems

Milad Fathi[a,*], M.R. Mozafari[b] and M. Mohebbi[a]

[a]Department of Food Science and Technology, Ferdowsi University of Mashhad, PO Box: 91775-1163, Iran
(e-mail: milad.fathi@stu-mail.um.ac.ir)

[b]Australasian Nanoscience and Nanotechnology Initiative, Monash University LPO, P.O. Box 8052, Wellington Road, Clayton, Victoria 3800, Australia

Nanoencapsulation allows protection of the sensitive bioactive food ingredients from unfavorable environmental conditions, eradication of incompatibilities, solubilization, or masking of unpleasant taste or odor. This paper reviews the present state of the art of lipid based carriers including nanoemulsions, nanoliposomes, solid lipid nanoparticles (SLNs) and novel generation of encapsulation system namely nanostructure lipid carriers (NLCs) regarding their production method, physicochemical properties, functionalities, stabilization techniques, potential advantages and limitations and delivery mechanisms. In the last section, mathematical models for predication of bioactive release kinetics from lipid based nanocarriers, which can be applied for optimization of encapsulation systems, are presented and some future developments in the area of nanoencapsulation are discussed.

Introduction

Nanotechnology is defined as creation, utilization and manipulation of materials, devices or systems in the nanometer scale (smaller than 100 nm). In recent years nanotechnology has found innumerable applications in different food industries (Aguilera *et al*., 2008; Fathi & Mohebbi, 2010; Neethirajan & Jayas, 2010; Rizvi, Moraru, Bouwmeester, & Kampers, 2010; Sanguansri & Augustin, 2006). Some potential applications of this technology in nanoencapsulation and delivery of bioactive components have been documented in pharmaceutics, as well as cosmetics and food sciences (Farokhzad & Langer, 2009; Liu, Jiao, Wang, Zhou, & Zhang, 2008; Müller, Petersen, Hommoss, & Pardeike, 2007; Sagalowicz, Leser, Watzke, & Michel, 2006; Shah *et al*., 2007; Shimoni, 2009). Delivery system is defined as one in which a bioactive material is entrapped in a carrier to control the rate of bioactive release. Nanocarriers can protect a bioactive component from unfavorable environmental conditions e.g. oxidation and pH and enzymes degradation (Fang & Bhandari, 2010; Ghosh, Mandal, Sarkar, Panda, & Das, 2009; Zimet & Livney, 2009). Nanocarriers provide more surface area and have the potential to enhance solubility, improve bioavailability and ameliorate controlled release and targeting of the encapsulated food ingredients, in comparison to micro-size carriers (Mozafari, 2006a; Weiss, Gaysinsky, Davidson, & McClements, 2009).

Generally two controlled release mechanisms (Fig. 1) can be observed during delivery of a bioactive (Lakkis, 2007). (i) Delayed release, which is a mechanism by which the release of a bioactive substance is delayed from a bounded "lag time" up to a point when/where its release is preferred and is no longer obstructed. This mechanism could be used for flavor release in ready-meals, color release in beverages or protection of nutrition compounds in gastric condition and their release in the intestine.

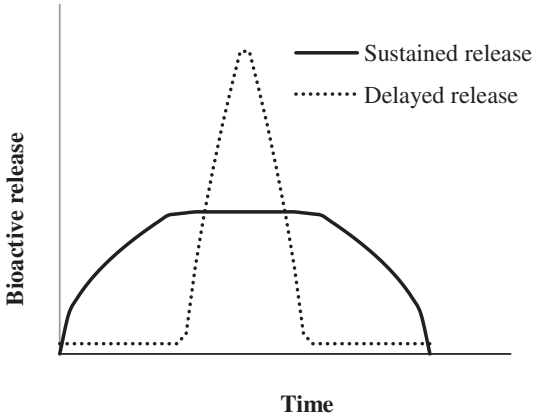

Fig. 1. Models of bioactive release from nanocarrier systems.

* Corresponding author.

0924-2244/$ - see front matter
doi:10.1016/j.tifs.2011.08.003

(ii) Sustained release, which is a mechanism engineered to keep constant concentration of a bioactive at its target site. This system can be employed for extending the release of the encapsulated material, including flavor or certain drugs such as insulin, in chewing gum. Many variables overshadow bioactive release of the encapsulated material. These include shape and dimensions of carrier, bioactive diffusivity and solubility in encapsulant and environmental media, erosion rate, polymorphism status of lipid based carriers, porosity and tortuosity, bioactive ratio between carrier and aqueous medium, encapsulation load (weight ratio of encapsulant to lipid) and loading efficiency (weight ratio entrapped to free encapsulant) and pH value of the medium (Barat, Crane, & Ruskin, 2008; Briones & Sato, 2010; Jalsenjak, 1992; Sant, Nadeau, & Hildgen, 2005; Siepmann, Faisant, & Benoit, 2002; Yang & Washington, 2006; Zhang, Yang, Chow, & Wang, 2003). Having a high encapsulation efficiency is always favorable, albeit encapsulation load more than 50% is not proper due to increase risk of bioactive leakage in case of more surface defect (Madene, Jacquot, Scher, & Desobry, 2006).

Typically, food applicable nanocarrier systems can be carbohydrate, protein or lipid based. Despite of different advantages of carbohydrate and protein based nanocapsules, they do not have potential of fully scale up due to requirement of applying different complicated chemical or heat treatments which cannot be completely controlled. On the other hand, lipid based nanocarriers have possibility of industrial production and bear advantage of more encapsulation efficiency and low toxicity. In this paper we will provide an overview of recent developments in different aspects (e.g. production methods, physicochemical properties, stabilization techniques, release mechanisms, advantages and disadvantages) of four famous lipid based carriers namely nanoemulsions, nanoliposomes, solid lipid nanoparticles (SLNs) and nanostructure lipid carriers (NLCs) (Table 1). In the last section of the paper, mathematical models for predication of bioactive release kinetics of lipid based nanocarriers are presented.

Nano delivery systems

Nanoemulsions

Nanoemulsions (also known as miniemulsions or submicron emulsions) are nanoscale droplets of multiphase colloidal dispersions formed by dispersing of one liquid in another immiscible liquid by physical share-induced rupturing (Liu, Sun, Li, Liu, & Xu, 2006; Mason, Wilking, Meleson, Chang, & Graves, 2006; Meleson, Graves, & Mason, 2004; Russel, Saville, & Schowalter, 1989). Different size ranges have been reported in the literature for nanoemulsions; e.g. less than 100 nm (Guo *et al*., 2007; Porras, Solans, Gonzلlez, & Gutiérrez, 2008; Shakeel & Ramadan, 2010), 10–100 nm (Talegaonkar, Mustafa, Akhter, & Iqbal, 2010), 100–500 nm (Anton, Benoit, & Saulnier, 2008; Constantinides, Chaubal, & Shorr, 2008; Rossi & Leroux, 2007; Tadros, Izquierdo, Esquena, & Solans, 2004; Unger *et al*., 2004) and 100–600 nm (Sakulku *et al*. 2009; Solans *et al*., 2003). However, the most appropriate ones based on nanotechnology definition is having size ranges of less than 100 nm and possessing different properties than ordinary emulsions. Nanoemulsions have some interesting physical properties that can be applied to distinguish them from microemulsions. For instance, microemulsions typically show multiple scattering of visible light, and therefore, have a white opaque appearance. In contrast, the droplet sizes in nanoemulsions are much smaller than visible wavelengths; hence most nanoemulsions appear optically transparent (McClements & Li, 2010; Shakeel & Ramadan, 2010). This is a very favorable feature of nanoemulsions for applying them as the nutrient carriers in beverages. Rheological properties of nanoemulsions are also different from micoemulsion. For example, Mason and Rai (2003) reported a rapid increase in the shear modulus of nanoemulsions by decreasing emulsion droplet size. Furthermore, at very high droplet volume fraction (φ), where the droplets commence to deform, the elastic shear modulus of repulsive emulsions was reported to be proportional to the Laplace pressure of the undeformed droplets leading to extraordinary elastic modulus of nanoemulsion. Likewise, at the same droplet volume fraction, nanoemulsions enhance shelf stability against the gravity over the microemulsions due to Brownian motion of nano sized droplets, caused by entropic driving forces (Mason *et al*., 2006). Unlike the microemulsions that are thermodynamically stable and form spontaneously, nanoemulsions are kinetically stable (Henry, Fryer, Frith, & Norton, 2010; Tadros *et al*., 2004). An interesting feature of nanoemulsions in contrast to microemulsions is that, they are metastable and can be diluted with water without change in the droplet size distribution (Gutieırrez, Gonzaılez, Sole', Pey, & Nolla, 2008).

Production method

The methods used to produce nanoemulsions can be divided into the mechanical and non-mechanical techniques. Mechanical (high-energy) methods include high-pressure homogenization, microfluidization and ultrasonication (Anton, Saulnier, Beduneau, & Benoit, 2007; Tadros *et al*., 2004).

To form a fine stable emulsion using high-pressure homogenization, the coarse dispersion of the oil and aqueous phase and emulsifier is passed through a small inlet orifice at pressures in the range of 500–5000 psi. Microfluidization uses a very high pressure (up to 20,000 psi) to force the liquid through the interaction chamber, which consists of microchannels of a special configuration. The emulsion feeds through the microchannels into a collision chamber which leads to formation of fine nano-scale emulsion droplets. The emulsification mechanism is based on combination of cavitation and mechanical shear. The operating pressure and the number of passing cycles of the coarse preemulsion in the microfluidizer or homogenizer have strong effect on the particle size of the formed

Table 1. Lipid based carrier systems and their features.

Lipid carrier system	Preparation technique	Physical morphology	Formulation	Advantage	Disadvantage	Example application
Nanoemulsion	(i) Mechanical method • Homogenization • Microfluidization • Ultrasonication (ii) Non-mechanical method • Solvent diffusion	Lipid	Aqueous phase, liquid (at processing and storage temperature) lipid phase and emulsifier	• Possibility of large-scale production • Delivery of poorly water-soluble ingredients	• Rapid release • Low stability in gastric condition	Encapsulation of water-insoluble bioactive food materials (Cheong *et al.*, 2008; Jafari *et al.*, 2008)
Liposome	(i) Mechanical method • Extrusion • Sonification • High pressure homogenization • Microfluidization • Colloid mill (ii) Non-mechanical method • Reversed-phase evaporation • Depletion of mixed detergent-lipid micelles • Heat treatment (Mozafari)	Liquid	Aqueous phase, liquid (at processing and storage temperature) lipid phase and amphiphilic compounds	• Possibility of large-scale production • Targetability • Delivery of poorly water-soluble, water-insoluble and amphiphilic ingredients	• Rapid release	Encapsulation of enzymes (Rao *et al.*, 1995), vitamins (Gonnet *et al.*, 2010), antimicrobials (Malheiros, Daroit, & Brandelli, 2010) and minerals (Arnaud, 1995)
Solid lipid nanoparticle (SLN)	(i) Mechanical method • Hot homogenization • Cold homogenization • Ultrasonication (ii) Non-mechanical method • Ultrasonic-solvent evaporation-emulsification	Solid	Aqueous phase, solid (at storage temperature) lipid phase and emulsifier	• High encapsulation efficiency • Possibility of large-scale production and sterilization • High flexibility in controlled release profile due to solid matrix • Targetability	• Recrystallization risk and possibility of explosion • Low encapsulation load	Encapsulation of water soluble and insoluble bioactive food materials (Jee, Lim, Park, & Kim, 2006; Jenning, Schäfer-Korting, & Gohla, 2000)
Nanostructure lipid carrier (NLC)	(i) Mechanical method • Hot homogenization • Cold homogenization • Ultrasonication (ii) Non-mechanical method • Ultrasonic-solvent evaporation-emulsification	Solid	Aqueous phase, solid and liquid (at storage temperature) lipid phase and emulsifier	• High encapsulation load • High stability (decrease risk of recrystallization) during storage	• Slightly faster release in comparison to SLN	Encapsulation of water soluble and insoluble bioactive food materials (Hentschel, Gramdorf, Müller, & Kurz, 2008; Kong, Xia, & Liu, 2011)

nanoemulsion (Constantinides *et al*., 2008; Maa & Hsu, 1999; Quintanilla-Carvajal *et al*., 2010). The mechanism of nanoemulsion generation using ultrasonication is attributed to bubble cavitation. However, this mechanism is not fully understood yet (Bondy & Sollner, 1935; Mason, 1992). The ultrasound waves (at ultrasonic frequencies typically 20 kHz or larger and high power intensity) result in sequential formation, growth and collapse of microscopic vapor bubbles in the liquid. Subsequently, the collapse of these cavities provides sufficient energy to increase surface area of droplets (Patil & Pandit, 2007). Efficiency of nanoemulsification by sonication (considering the size of the nanoemulsion droplets and required time to attain this size), depends both on the emulsion properties (lipid, encapsulated bioactive, surfactant and cosurfactant) and the power of the device (Leong, Wooster, Kentish, & Ashokkumar, 2009). Kentish *et al*. (2008) produced nanoemulsion using flax seed oil and tween 40 (C16) as an emulsifier by ultrasonication method. Results showed that there is an optimum power input level above which droplet coalescence and cavitational bubble cloud formation adversely affect the efficiency, reproducibility, quality of nanoemulsion production. Increasing sonication time reduces droplet sizes to a point, but continued sonication more than one to five minutes is useless. The produced nanoemulsions are comparable to those emulsions prepared using a microfluidizer operated at 100 MPa. In spite of high potential of sonication for research purposes, it does not appear to be practical for industrial applications. In this case using high-pressure homogenizer or microfluidization are often preferred (Samer & Schork, 1999). It is remarkable that when the aim of the processing is the encapsulation of sensitive molecules such as enzymes, using ultrasonication and high-pressure homogenization may cause degradation, denaturation or loss of activity of the bioactive agents (Anton *et al*., 2008). Pinnamaneni, Das, and Das (2003) compared oil/water submicron emulsions manufactured by microfluidization and homogenization methods. The microfluidization was found to be more effective than the homogenization, since submicron emulsions prepared by this process had smaller droplet diameters and exhibited less droplet diameter growth over time. Jafari, He, and Bhandari (2006) studied the efficiency of producing nanoemulsions using sonication and microfluidization techniques. Their results showed that, whether both methods were able to form nanoemulsions of the sizes ranging from 150 to 700 nm, the microfluidizer produced emulsions with restricted size distributions and sonication was more commodious regarding to operation control and cleaning. Jafari, Assadpoor, Bhandari, and He (2008) produced nanoemulsion using microfluidization and ultrasonication for encapsulation of fish oil. Their results showed that microfluidization is a competent emulsification technique leading to fish oil-encapsulated powder with the lower unencapsulated oil at the surface of particles in comparison to ultrasonication method.

Nanoemulsions can be formed using non-mechanical methods; e.g. solvent diffusion technique (Anton *et al*., 2007; Tadros *et al*., 2004; Unger *et al*., 2004). Cheong, Tan, Man, and Misran (2008) applied emulsification–evaporation technique to prepare nanoemulsion (90–120 nm) of α-tocopherol. In this method α-tocopherol is first dissolved in an organic solvent. The resulting coarse dispersion is passed through a high pressure homogenizer and then the solvent is removed from fine emulsion by evaporation (Jaiswal, Gupta, & Kreuter, 2004; Mainardes & Evangelista, 2005). However, the α-tocopherol content of prepared nanoemulsion was significantly decreased during storage. Lee and McClements (2010) produced oil/water nanoemulsions coated by whey protein using combination of emulsification, solvent displacement and/or solvent evaporation approaches. A limitation of this approach is the requirement of large amounts of organic solvent to prepare emulsions and consequently the necessity of using expensive equipment to remove organic solvent before consumption. Generally, due to use of organic solvent, application of low energy methods is limited in food sectors.

Applications and features

Nanoemulsions are good candidate for delivery of poorly water-soluble food ingredients, such as fish oil and lipophilic vitamins, because of their ability to improve bioactive solubilization and potential for enhancing absorption in the gastrointestinal (GI) tract, caused by surfactant induced permeability changes. After ingestion, droplets readily disperse in stomach to small droplet of nanoemulsion, which promotes wide distribution of the encapsulated bioactive throughout the GI condition (Talegaonkar *et al*., 2010). Yuan, Gao, Mao, and Zhao (2008) found that the optimum production conditions for the preparation of β-carotene nanoemulsions are a homogenization pressure of 129 MPa; a homogenization temperature of 47 °C; a β-carotene concentration of 0.82% and an emulsifier concentration of 8.2%. Soybean oil-based nanoemulsion has been shown to have bactericidal properties against Gram-positive bacteria (Hamouda & Baker, 2000) and fungistatic, but not fungicidal, property (Hamouda *et al*., 2001). Teixeira *et al*. (2007) prepared BCTP nanoemulsion (an O/W nanoemulsion of soybean oil and tri-n-butyl phosphate emulsified with Triton X-100) and showed that it was effective in reducing the cell numbers of *Listeria monocytogenes*.

Wulff-Perez, Torcello-Gomez, Galvez-Ruız, and Martın-Rodrıguez (2009) reported that destabilization of the nanoemulsions takes place above certain surfactant concentration. This phenomenon can be described as a depletion–flocculation effect caused by non-adsorbed micelles. They presented a theoretical mathematical model based on experimental parameters to determine the optimum value of surfactant concentration. A bioactive material might have different localizations within an emulsion (Fig. 2), and this localization can obviously be influenced by the production

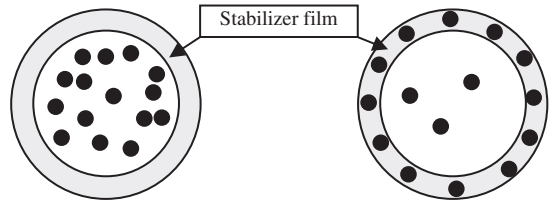

Fig. 2. Principles of chemical stabilization of bioactive ingredient encapsulated in nanoemulsion. Applying Low temperature and low number of homogenization cycles (Left) lead to localization of the bioactive more toward the inner oil phase (bioactive is not protected against chemical degradation). Increasing temperature and homogenization cycles (right) allow diffusion of the bioactive into the outer stabilizer film (more protection against chemical degradation) (Baspinar, *et al.*, 2010).

parameters, e.g. number of homogenization cycles and production temperature. The location of a drug, or any other bioactive compound, within the capsule or carrier influences the stability, release and thus the bioavailability of the nanocarrier formulation. Baspinar, Keck, and Borchert (2010) prepared a nanoemulsion formulation, using polysorbate and less purified egg lecithin as emulsifiers, through the high pressure homogenization method. Interestingly, their results showed that the highest chemical stability was obtained with low homogenization pressures but higher numbers of homogenization cycles and higher temperatures (e.g. 300 bar, 10 cycles and 50 °C). This could be attributed to an immigration of the bioactive from inner oil to the stable surfactant outer layer. However, the release profiles of these nanoemulsions were not investigated.

Maruno and da Rocha-Filho (2010) produced non-food grade nanoemulsion using lipophilic (Sorbitan monooleate; HLB = 4.3) and hydrophilic (Ceteth-10, HLB = 12.9) surfactants. The accelerated tests based on measurement of zeta potential showed that nanoemulsions are stable for 15 years. It was demonstrated that nanoemulsions stabilized by lecithin/polyol or lecithin/carbohydrate matrix have droplet sizes ranging from 30 to 60 nm. In other studies, it was shown that the bioavailability of the nanoemulsion-encapsulated vitamin E was 10-fold more than the bioavailability of the same vitamin contained in commercial gelatin capsules (Gonnet, Lethuaut, & Boury, 2010; Wajda, 2003; Wajda, Zirkel, & Schaffer, 2007).

Nanoemulsions have low stability in acidic conditions. Klinkesorn and McClements (2009) applied chitosan for enhancing the stability of nanoemulsions. Their results showed that the zeta potential of the oil droplets in lecithin-chitosan stabilized nanoemulsions changed from positive to negative and the emulsions droplets can be degraded by lipase under simulated GI conditions. Therefore, chitosan-coated lipid droplets can be potentially applied as useful carriers for the oral delivery of lipophilic compounds.

Finally, it should be mentioned that advantages of nanoemulsions include toxicological safety and a high content of the lipid phase as well as the possibility of large-scale production using high-pressure homogenization (HPH). However, controlled drug release from nanoemulsions is very unlikely because of the small size and the liquid state of the carrier.

Liposome

Having a number of benefits, e.g. possibility of large-scale production using natural ingredients and entrapment and release of water-soluble, lipid-soluble, and amphiphilic materials as well as targetability (Huwiler, Kolter, Pfeilschifter, & Sandhoff, 2000; Mozafari, Johnson, Hatziantoniou, & Demetzos, 2008; Thompson, Hindmarsh, Haisman, Rades, & Singh, 2006), liposomes have been widely used in food sector both in research and industry. Notable examples are liposome formulations of antimicrobials (Malheiros, Daroit, & Brandelli, 2010; Malheiros, Daroit, Silveira, & Brandelli, 2010; Taylor, Bruce, Weiss, & Davidson, 2008; Taylor, Davidson, Bruce, & Weiss, 2005b; Taylor, Gaysinsky, Davidson, Bruce, & Weiss, 2007; Were, Bruce, Davidson, & Weiss, 2004; Were, Bruce, & Weiss, 2003), lipophilic vitamins (Gonnet *et al.*, 2010; Padamwar & Pokharkar, 2006), enzymes (Dufour, Laloy, Vuillemard, & Simard, 1996; Rao, Chawan, & Veeramachaneni, 1995) and minerals (Arnaud, 1995). Similar to nanoemulsions, liposomes are kinetically stable. The mechanism of liposome formation is based on the unfavorable interactions occur between amphiphilic compounds (mainly phospholipids) and water molecules, where the polar head groups of phospholipids are subjected to the aqueous phases of the inner and outer media, and the hydrophobic hydrocarbon tails are associated into the bilayer and spherical core shell structures are formed (Goyal *et al.*, 2005; Jesorka & Orwar, 2008).

Liposomes can be produced using natural ingredients on an industrial scale and have the capability of entrapping materials with different solubilities (Mozafari & Khosravi-Darani, 2007; Yurdugul & Mozafari, 2004). Another important advantage of liposomes (also known as lipid vesicles) is targetability. Lipid vesicles can be tailored to deliver and release their load in the target site inside and outside the body (Mozafari, 2006b).

Production method

Different procedures have been developed to produce nano-sized liposomes. These include mechanical (extrusion, where the liposomes are forced through filters with well defined pore sizes under moderate pressures, sonification, high pressure homogenization, microfluidization and colloid mill) and non-mechanical (reversed-phase evaporation and depletion of mixed detergent-lipid micelles) methods (Chonn & Cullis, 1998; Gregoriadis, 1993; Mui & Hope, 2007; Schroeder, Kost, & Barenholz, 2009; Watwe & Bellare, 1995). It was reported that induced mechanical shear by ultrasonic cavitation, results in the narrow

size distribution of droplets (Maulucci *et al*., 2005; Moran *et al*., 2006; Pereira-Lachataignerais *et al*., 2006). There are several recent articles that describe methods of liposome preparation in detail (Gregoriadis, 2007; Mozafari, 2010; Taylor, Davidson, Bruce, & Weiss, 2005a).

A method for liposome preparation is presented by Mozafari based on heating treatment (Mozafari, 2005a, 2005b; Mozafari, Reed, Rostron, Kocum, & Piskin, 2002). In this technique the liposomal ingredients are added to a preheated mixture of bioactive compound and glycerol (about 60 °C). The mixture is further heated while stirring under nitrogen atmosphere. At this stage multilamellar vesicle liposomes (MLV) are formed. If nano-sized vesicles (nanoliposomes) required, the samples are then consecutively extruded through membrane filters above the phase transition temperature (T_c) of the liposomes. Finally, the product is left at a temperature above T_c under nitrogen to be stabilized. Colas *et al*. (2007) applied this method for the preparation of nanoliposomes for the encapsulation of nisin Z. Their results showed that stability of nanoliposome-encapsulated nisin enhanced for at least 14 months for the vesicles stored at 4 °C and for 12 months for those stored at 25 °C.

More recently, a further developed method was introduced by the group of Mozafari through which nano-sized vesicles and a number of nanocarrier systems (e.g. Archaeosomes, nanocochleates, niosomes) can be manufactured in a single step using a single vessel, without employing toxic solvents (Khosravi-Darani, Pardakhty, Honarpisheh, Rao, & Mozafari, 2007; Mozafari & Khosravi-Darani, 2007; Patel & Chen, 2006; Sahin, 2007).

Applications and features

Liposomes are classified based on their number of bilayers and size. According to their bilayer structure, vesicles can be classified as unilamellar vesicles (ULV), multilamellar vesicles (MLV) that consist of one or more concentric lipid bilayer(s) (Nagle & Tristram-Nagle, 2000; Yung, Shek, & Stanacev, 1985). Another type of liposomes is known as multivesicular vesicles (MVV), which includes some small non-concentric vesicles entrapped within a single lipid bilayer. Vesicles can be further categorized by their size, as small unilamellar vesicle (SUV) characterized by diameters ranging between 20 and 100 nm with a narrow size distribution, and large unilamellar vesicle (LUV) with particle sizes reaching up to few micrometers. SUVs are generally formed by sequential delamination of the outer layers of MLV (Barenholz *et al*., 1977; Zasadzinski, 1986). SUVs have a low aqueous core volume to lipid ratio; thus they are not efficient encapsulants of large functional foods and nutraceutical compounds (Sharma & Sharma, 1997). However, nano-sized liposomes have the ability to entrap hydrophilic molecules in their interior volume, and hydrophobic compounds in the hydrophobic part of the lipid bilayer, simultaneously (Acosta, 2008; Mozafari & Mortazavi, 2005). On the other hand, LUVs and MVVs, which have a large aqueous core volume to lipid ratio; can carry large loads of encapsulated water-soluble compounds in their internal core and therefore are more appropriate for the encapsulation of large hydrophilic compounds (Augustin, Sanguansri, Margetts, & Young, 2001; Gibbs, Kermasha, Alli, & Mulligan, 1999). In contrast to ULVs, MVVs provide sustained release profile of the encapsulated material (Ye, Asherman, Stevenson, Brownson, & Katre, 2000). Compared to other encapsulation technologies, liposomes can generally provide higher chemical stability and protection to sensitive bioactives such as ascorbic acid and glutathione at high water-activity conditions (Kirby, 1993; Suntres & Shek, 1996).

Temperature-sensitive liposomes (also known as thermo-sensitive liposomes) can be produced by modification of the lipid bilayers with specific polymers. The polymer should have a critical temperature at which it turns to water-soluble below and becomes water-insoluble above that temperature. The polymer-coated liposomes are destabilized above the critical temperature due to interaction between the liposome membrane and the hydrophobic polymer chains, leading to release of the encapsulated material (Hayashi, Kono, & Takagishi, 1996; Kitano, Maeda, Takeuchi, Ieda, & Aizu, 1994; Kono, Hayashi, & Takagishi, 1994; Kono, Nakai, Morimoto, & Takagishi, 1999). These kinds of carriers are ideal for flavor release by increasing cocking temperature of the ready meals.

Recent studies showed that pH-sensitive liposomes can be prepared using amphiphilic lipid molecules such as unsaturated phosphatidylethanolamine (PE) and oleic acid which destabilize the liposome at the acidic condition and release the encapsulated bioactive (Cho *et al*., 2009). More, it has been shown that pH-sensitive polymers (e.g. poly methacrylic acid-co-stearyl methacrylate) can be added to liposomes by mixing lipids and polymers during the preparation of vesicles. Hence, the stimulus-responsive function of these liposomes chiefly depends on the structural properties of the polymer surrounding the outer surface of the vesicles (Sudimack, Guo, Tjarks, & Lee, 2002; Zignani, Drummond, Meyer, Hong, & Leroux, 2000). To our knowledge, the pH-sensitive liposomes have not been employed in the encapsulation of food ingredients to date. However, it seems they have significant potential in food industry for example for the release of antimicrobials upon pH changes as a result of increased microbial activity.

Many methods for the stabilization of liposomes have been investigated. These include lyophilization, freezing, spray-drying and supercritical fluid (SCF) technology (Kadimi, Balasubramanian, Ganni, Balaraman, & Govindarajulu, 2007; Lo, Tsai, & Kuo, 2004; Mishima, 2008). It was shown that the stability of liposomes produced using SCF is more than ones manufactured applying ultrasonication method (Kadimi *et al*., 2007). It might be due to the contamination of the liposomes with the probe sonicator which is the major drawback ultrasonication method. However, among these methods of stabilization,

lyophilization is the main approach used to prolong the shelf-life of liposomes, especially for liposomes containing thermosensitive compounds (Chen, Han, Cai, & Tang, 2010). In this case, addition of lyoprotectants is essential to avoid phase transition and loss of the encapsulated bioactive from the liposomes. Many sugars have been used as lyoprotectants during lyophilization, including monosaccharides, disaccharides, polysaccharides and synthetic saccharides. It is should be noted that trehalose usually exhibits the best protective effect among the disaccharides (Heikal *et al*., 2009; Kawai & Suzuki, 2007).

In spite of having different advantages, nanoliposomes have short release time. To overcome this limitation, chitosan coating can be employed by dropwise addition of chitosan solution to the liposome dispersion (Zaru, Manca, Fadda, & Antimisiaris, 2009). Research in the fields of pharmaceutical and food sciences showed that chitosan coating changed the liposome surface charge and slightly increased its particle size, while the liposome displayed a prolonged *in vitro* release profile and an enhanced stability (Laye, McClements, & Weiss, 2008; Li *et al*., 2009). The use of long chain saturated acyl chains (such as disteroylphosphatidylcholine) or hydrogenated soy phosphatidylcholine and the presence of an optimal level of cholesterol in the liposome membrane minimize membrane defects. Moreover, cholesterol dries the lipid–water interface, which leads to the enhancement of the chemical stability of the liposomal membrane against peroxidation and acyl ester hydrolysis (Parasassi, Di Stefano, Loiero, Ravagnan, & Gratton, 1994; Samuni, Lipman, & Barenholz, 2000). Liposomes coated with polyethylene glycol have been found to be resistant to digestion by bile salts (Iwanaga *et al*., 1999; H. Li, Song, Park, & Han, 2003) and are therefore useful for increasing the bioavailability of the encapsulated nutritional compounds.

Solid lipid nanoparticles (SLN)

Solid lipid nanoparticles (SLN) have attracted increasing scientific and commercial attention during the last few years in pharmaceutical and food sciences (Awad *et al*., 2008; Gallarate, Trotta, Battaglia, & Chirio, 2009; Taylor *et al*., 2007; Varshosaz *et al*., 2010; Varshosaz, Tabbakhian, & Mohammadi, 2009). SLNs are particles consisting of a matrix made of solid lipid shell (Müller, Dingler, Schneppe, & Gohla, 2000). Compared to nanoemulsions and liposomes, SLNs have some distinct advantages (Mäder & Mehnert, 2005; Mehnert & Mader, 2001; Müller & Runge, 1998; Saupe & Rades, 2006), which include:

- Having high encapsulation efficiency.
- Avoiding use of organic solvents in their preparation.
- Possibility of large-scale production and sterilization.
- Providing high flexibility in controlling the release profile due to solid matrix.
- Slower degradation rate allows bioactive release for prolonged times.
- The solid matrix can (but need not) protect the incorporated bioactive ingredients against chemical degradation.

In support of above advantages, it should be mentioned that bioactive ingredient release from nanoemulsions, which takes place based on the partitioning coefficient and the phase ratios of oil and water phases, is too fast (Washington, 1998). Longer release times can be achieved with liposomes. However, it is not yet appropriate for delivery of bioactive food ingredients. Compared to these carriers, release period for SLN is longer because of increase of degradation time of solid matrix. Solid matrix is able to provide more protection against chemical reactions such as oxidation (Müller *et al*., 2000).

Production method

Several methods have been reported for SLN production in pharmaceutics (Schäfer-Korting & Mehnert, 2005). However, only two basic production techniques are likely to be used for large-scale production of SLN in food processing: (i) Hot homogenization and (ii) Cold homogenization (Müller *et al*., 2000; Müllers, Schwarz, Mehnert, & Lucks, 1993).

In hot homogenization method, the lipid is melted at approximately 5–10 °C above its melting point, the bioactive compound is dissolved in the melted lipid and the produced liquid is dispersed in an aqueous surfactant solution with the same temperature. The obtained emulsion is then passed through a high-pressure homogenizer at the controlled temperature. The result of this process is a hot O/W emulsion. Cooling of the emulsion leads to the recrystallization of the lipid and the formation of solid lipid nanoparticles. Recrystallization can also be initiated by lyophilization (Müller, Mader *et al*., 2000). Due to loss of hydrophilic bioactive ingredients to the water phase, the hot homogenization technique cannot efficiently be employed to incorporate these components into solid matrix. On the other hand, this method cannot be applied for ultra heat sensitive food components such as enzymes. Cold homogenization can be applied to overcome these obstacles. Similar to the hot homogenization technique, the bioactive compound is incorporated into a melted lipid. Then the lipid melt is cooled and after solidification grounded by a mortar mill. The obtained lipid microparticles are dispersed in a cold surfactant solution at room temperature. The produced lipid suspension is then homogenized at room temperature, or even lowers (e.g. 0 °C). The solid state of the matrix minimizes partitioning of the drug to the water phase. In this method special care must be taken due to temperature increase during homogenization (e.g. 10–20 °C per homogenization cycle) and milling. A major problem with delivery of actives using solid lipid nanoparticles is the burst release which is due to the presence of bioactive compounds in the outer shell. Using low production temperature and low surfactant concentration lead to decrease the burst effect (Müller, Radtke, & Wissing,

2002b; zur Mühlen, Schwarz, & Mehnert, 1998). Recently, Weiss *et al.* (2008) reviewed important parameters (e.g. lipid composition, surfactant type, surfactant concentration, droplet size and cooling conditions) affecting the structure and properties of SLN prepared for the delivery of bioactive food components.

SLNs can also be prepared easily on laboratory scale by emulsification-evaporation followed by sonification method. In this technique, coarse emulsion is formed by mixing oil phase, organic solvent, emulsifier and bioactive component. The pre-emulsion is then sonicated at a temperature above the melting point of lipid for appropriate period of time. Finally, the SLNs are produced by adding the resultant nanoemulsion to cold water containing surfactant and mixing to allow solvent evaporation (Varshosaz *et al.*, 2010, 2009; Varshosaz *et al.*, 2010).

Applications and features

Generally, there are three models for the incorporation of bioactive components into SLNs: (i) Homogeneous matrix model; (ii) Bioactive-enriched shell model; and (iii) Bioactive-enriched core model. The type of obtained model depends basically on the formulation components (lipid, lipophilic or hydrophilic bioactive compound and surfactant) and the production conditions (hot or cold homogenization). A homogeneous matrix (Fig. 3a) is mainly obtained when applying the cold homogenization method and when incorporating very lipophilic actives into SLNs with the hot homogenization technique. Release of the bioactive compound in this model is based on dissolution mechanism. A bioactive-enriched shell (Fig. 3b) might be obtained if phase separation occurs during the cooling process from the liquid oil droplet. This model shows a burst release behavior. A bioactive-enriched core (Fig. 3c) can be formed while the opposite phenomenon of bioactive-enriched shell model comes about, which means the bioactive compound starts precipitating first and therefore, the shell have less encapsulated components. This structure model leads to a membrane controlled release governed by the Fick's law of diffusion (see Section 3) (Müller *et al.*, 2002b).

An important parameter affecting physical stability of colloidal dispersion is surface charge that can be quantified by zeta potential (Bunjes, 2005; Cavalli, 1997; Lim & Kim, 2002). In general (but not always), nanoparticle aggregation is less likely to come along for charged particles (high values of zeta potential) due to electric repulsion (Mehnert & Mader, 2001; Wissing & Müller, 2002). The gastrointestinal environment (ionic strength and strong pH changes) may destabilize the particles and lead to aggregation and size growth. Zimmermann and Müller (2001) reported that it is possible to produce stable SLNs in GI condition. SLNs are required to have zeta potentials larger than 8–9 mV in combination with steric stabilization that can be achieved by optimizing surfactant composition.

Solubility of bioactive compounds in melted lipid, chemical and physical structures of solid lipid matrix and polymeric state of lipid material are important factors affecting loading capacity of the carrier system. Adding solubilizers such as mono and diglycerides in the lipid mixture boosts bioactive solubilization and consequently increases loading capacity. The chemical structure of the lipid is also critical; for example applying lipids which form highly crystalline particles with a perfect lattice (e.g. monoacid triglycerides) lead to expulsion of bioactive ingredient (Westesen, Bunjes, & Koch, 1997). Crystallization of the lipid in nanoparticles is different compared to the bulk material. Lipid nanoparticles recrystallize at least partially in the α-form, whereas bulk lipids tend to recrystallize preferentially in the β′-modification and transform rapidly into the β-form (Westesen, Siekmann, & Koch, 1993). Production of stable SLN suspensions requires delaying of the α to β polymorphic transition (e.g. by changing fat type or surfactant surface coverage using surfactants with hydrocarbon tails that crystallize prior to the lipid phase), preventing of particle aggregation by increasing zeta potential as well as storing at low temperatures (Awad *et al.*, 2008; Helgason, Awad, Kristbergsson, McClements, & Weiss, 2009a, 2009b).

Lippacher and his coworkers (Lippacher, Müller, & Mader, 2004; Lippacher, Müller, & Mؚ; der, 2002) studied rheological properties of a non-food semisolid, containing SLNs. Their results proved that the existence of SLNs is a prerequisite to form a semisolid dispersion having the appropriate consistency and elastic modulus. Rheological features have strong effects on sensory and physical

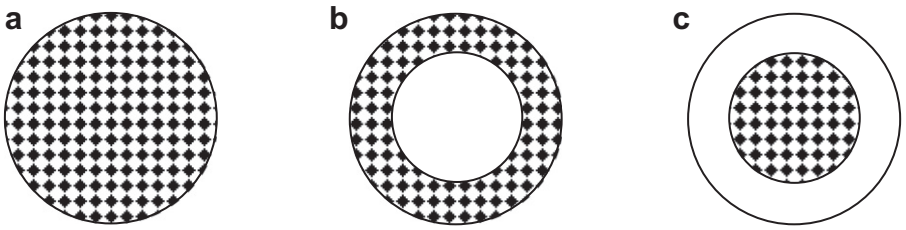

Fig. 3. Structural models for the incorporation of bioactive components into SLNs.

properties of food systems. However, to date there is no published data on rheological properties of food systems containing SLNs.

It has been shown that particle size of aqueous SLN dispersions might be stable over 12–36 months (Mehnert & Mader, 2001). Nevertheless, an increase in particle size and instability may occur during the storage of SLN dispersion. Lyophilization is a promising technique to improve chemical and physical stability of SLN. However, freezing of the sample might cause instability due to the freezing out effect which results in changes of the osmolarity and zeta potential. This impediment can be overcome by using cryoprotective agents such as sorbitol, mannose, trehalose and glucose that decrease the osmotic activity of water and favor the glassy state of the frozen sample (Crowe *et al.*, 1986; Hauser & Strauss, 1988; Schwarz & Mehnert, 1997). Spray drying has been rarely used as an alternative method to lyophilization for increasing the stability of SLNs (Freitas & Müller, 1998). However, due to the possibility of aggregation as a result of applying high temperature and shear forces, using high melting-point lipids (higher than 70 °C) is recommended (Mehnert & Mader, 2001).

Nanostructure lipid carrier (NLC)

In spite of having different advantages, SLNs have some potential problems such as low encapsulation load and possibility of explosion during storage. With increasing the purity of applied lipid, less space is available to accommodate drug and nutraceutical molecules, hence encapsulation efficiency decreases and explosion risks increases due to formation of α and β′ into perfect β transition form (Westesen *et al.*, 1997).

Radtke and Müller (2001) developed a novel carrier namely nanostructure lipid carrier (NLC) for overcoming the limitations of SLNs. NLC can be produced by mixing very different lipid molecules i.e. solid lipids with liquid lipids (oils) based on preparation methods described for SLN. The produced matrix of the lipid particles demonstrates a melting point depression compared to the original solid lipid. In fact by giving the lipid matrix a certain nanostructure, the encapsulation load of bioactive ingredient is enhanced and expulsion phenomenon during storage is limited by preventing the formation of perfect crystals (Chen *et al.*, 2010; Müller, Radtke, & Wissing, 2002a; Müller *et al.*, 2002b). It is also reported that NLCs have smaller particle sizes compared to SLNs (Fang, Fang, Liu, & Su, 2008). A pharmaceutical study by Teeranachaideekul, Müller, and Junyaprasert (2007) for the investigation of chemical stability enhancement of ascorbyl palmitate (AP) after incorporation into NLCs showed that addition of antioxidants as well as selection of suitable surfactants and solid lipids improved the chemical stability of AP. Investigation physicochemical properties proved that NLCs have zeta potentials ranging from −13.4 to −23.5 and show a sustained release mechanism and no obviously burst release in gastrointestinal condition (Zhuang *et al.*, 2010). This study demonstrates the possibility of NLC application for the encapsulation of lipophilic nutrients such vitamin E and omega 3 fatty acids.

Modeling bioactive release of nanoscale delivery systems

Towards augmenting the controlled delivery systems, mathematical modeling of the release process plays an important role as it demonstrates the mechanism(s) of bioactive release, provides a scenario for the optimization of the carrier systems and avoids excessive experimentation. Generally, the bioactive release is governed by one or combination of three different mechanisms, i.e. (i) diffusion; (ii) erosion; and (iii) swelling. However, the two latter ones are more likely to occur in hydrophilic (carbohydrate and protein based) carriers. Therefore, the mathematical models regarding the diffusion mechanism are discussed for lipid based nanocarriers. The process of mass transfer kinetic in nanocarriers can be modeled using Fick's lows of diffusion. The Fick's first low (Eq. (1)) assumes constant diffusion coefficient and boundaries. The independency of diffusion to concentration is not correct in real situations. The concentration dependence of the diffusion coefficient of the bioactive can be written as the Fick's second low (Eq. (2)). Fick's equations can be solved analytically or numerically.

$$\frac{\partial c}{\partial t} = D\frac{\partial^2 c}{\partial z^2} \tag{1}$$

$$\frac{\partial c}{\partial t} = \frac{\partial}{\partial z}\left[D(c)\frac{\partial c}{\partial z}\right] \tag{2}$$

where c is the concentration of the bioactive compound, t is time, z is the position in the carrier and D is the diffusion coefficient of the bioactive ingredient. Higuchi (1963) developed a square root of time model to describe release phenomenon from spherical devices carrying a bioactive component:

$$M_t = \sqrt{Dc_m(2c_t - c_c)t} \tag{3}$$

In this expression, c_m is the solubility of the bioactive in the encapsulant matrix, c_t the initial bioactive concentration, and c_s is the solubility of bioactive in the sink phase. An approximate relation derived from the Higuchi equation describes the release of a dispersed solute from a rigid matrix of the spherical shaped carriers where there is no swelling or erosion mechanisms can be written as:

$$M_t = 4r^2\pi\left[\sqrt{2(c_0 - c_s)Dc_s t} - \frac{4c_s D}{9r}\left(\frac{c_s}{2c_0 - c_s} - 3\right)t\right] \tag{4}$$

where, c_0 is initial bioactive concentration. In large values of release time (t) the portion of the second term becomes significant, and hence the particle size of the encapsulation

system becomes important. Another form of Higuchi model can be written based on Eq. (5):

$$J = [2Dc_s\varepsilon(c_m - 0.5c_s\varepsilon)]^{0.5} \times t^{0.5} = k_H\sqrt{t} \quad (5)$$

where J is the amount of bioactive released in time t, ε is the porosity and k_H is the Higuchi constant. The above equation can be expressed as:

$$\frac{M_t}{M_\infty} = k_H \times \sqrt{t} \quad (6)$$

Thus, the bioactive release rate is proportional to the inverse of the square root of time. Haidar, Hamdy, and Tabrizian (2008) used this model for the investigation of bovine serum albumin release kinetics from alginate and chitosan-coated liposomes. The results showed high ability of this model to kinetically investigate the release rate. Based on this model two distinct regions were observed, which were related to the initial phase (shell release) and a terminal phase (core release). Abdel-Mottaleb, Neumann, and Lamprecht (2010) showed zero order like release kinetics (Fick's first low) can be used for modeling of bioactive release from lipid nanocapsules. The fluxes were calculated and found to increase from 1.5 to 7.0 ($\mu g \times cm^{-2} \times min^{-1}$) with increasing the temperature from 4 to 50 °C.

The release kinetics can also be modeled using monoexponential (Eq. (4)) and biexponential (Eq. (8)) equations.

$$C = C_0 e^{-kt} \quad (7)$$

$$C = ae^{-k_1 t} + be^{-k_2 t} \quad (8)$$

The release rate constants are k, k_1 (related to burst phases) and k_2 (related to sustained phases) and the initial bioactive concentrations are C_0, a (for burst phases) and b (for sustained phases). Based on the values of a and b the value of the bioactive entrapped within the nanocarrier can be determined. Mathematical modeling of the release profiles for non-food bioactives was conducted according to these equations. The results showed that presence of the polymer increases the half-lives of the burst phases (2.7 min) while the presence of the oil phase increases the half-lives of the sustained phases (147.5 min) of nanoemulsions (Cruz *et al.*, 2006). In spite of the importance of release kinetic modeling in nanoencapsulated food ingredients, the numbers of published data are scarce.

Concluding and future remarks

Despite the strong upsurge in the investigations of nano-delivery systems and proven role of nanoencapsulation in enhancing bioavailability, solubility and protection of food ingredients, there is no comprehensive information on different aspects of lipid-based nanocarriers. In this paper we attempted to provide an overview of latter developments of four lipid based encapsulation systems namely nanoemulsions, liposomes, solid lipid nanoparticles and nanostructure lipid carriers. Recent studies revealed that applying the two latter nanocarriers have considerable advantages such as having more stability, longer release time and sustained release profile over the conventional encapsulation systems. However, future trends in nano-delivery systems should focus more on investigations pertaining to the physicochemical properties of the nanocarriers as well as the properties and interactions of food systems incorporating nanoencapsulated bioactives. On the other hand, more studies are necessary for modeling the release kinetics of nanoencapsulated food components using the available equations as well as the recent novel models. This comprises one of the future objectives of our research team.

References

Abdel-Mottaleb, M. M. A., Neumann, D., & Lamprecht, A. (2010). In vitro drug release mechanism from lipid nanocapsules (LNC). *International Journal of Pharmaceutics, 390*, 208–213.

Acosta, E. (2008). Testing the effectiveness of nutrient delivery systems. In N. Garti (Ed.), *Delivery and controlled release of bioactives in foods and nutraceuticals*. Boca Raton: CRC Press.

Aguilera, J. M., Lillford, P. J., Lee, J., Wang, X., Ruengruglikit, C., Gezgin, Z., et al. (2008). Nanotechnology in food materials research. In: *Food materials science* (pp. 123–144). New York: Springer.

Anton, N., Benoit, J. P., & Saulnier, P. (2008). Design and production of nanoparticles formulated from nano-emulsion templates—a review. *Journal of Controlled Release, 128*, 185–199.

Anton, N., Saulnier, P., Beduneau, A., & Benoit, J.-P. (2007). Salting-out effect induced by temperature cycling on a water/nonionic surfactant/oil system. *The Journal of Physical Chemistry B, 111*, 3651–3657.

Arnaud, J. P. (1995). Pro-liposomes for the food industry. *Food Technology in Europe, 2*, 30–34.

Augustin, M. A., Sanguansri, L., Margetts, C., & Young, B. (2001). Microencapsulation of food ingredients. *Food Australia, 53*, 220–223.

Awad, T. S., Helgason, T., Kristbergsson, K., Decker, E. A., Weiss, J., & McClements, D. J. (2008). Effect of cooling and heating rates on polymorphic transformations and gelation of tripalmitin solid lipid nanoparticle (SLN) suspensions. *Food Biophysics, 3*, 155–162.

Barat, A., Crane, M., & Ruskin, H. J. (2008). Quantitative multi-agent models for simulating protein release from PLGA bioerodible nano- and microspheres. *Journal of Pharmaceutical and Biomedical Analysis, 48*, 361–368.

Barenholz, Y., Gibbes, D., Litman, B. J., Goll, J., Thompson, T. E., & Carlson, R. D. (1977). A simple method for the preparation of homogeneous phospholipid vesicles. *Biochemistry, 16*, 2806–2810.

Baspinar, Y., Keck, C. M., & Borchert, H. H. (2010). Development of a positively charged prednicarbate nanoemulsion. *International Journal of Pharmaceutics, 383*, 201–208.

Bondy, C., & Sollner, K. (1935). On the mechanism of emulsification by ultrasonic waves. *Transactions of the Faraday Society, 31*, 835–843.

Briones, A. V., & Sato, T. (2010). Encapsulation of glucose oxidase (GOD) in polyelectrolyte complexes of chitosan-carrageenan. *Reactive and Functional Polymers, 70*, 19–27.

Bunjes, H. (2005). Characterization of solid lipid nano and microparticles. In: *Lipospheres in drug targets and delivery*. CRC Press.

Cavalli, R.e.a. (1997). Sterilization and freeze-drying of drug-free and drug-loaded solid lipid nanoparticles. *International Journal of Pharmecutical, 148*, 47.

Chen, C.-C., Tsai, T.-H., Huang, Z.-R., & Fang, J.-Y. (2010). Effects of lipophilic emulsifiers on the oral administration of lovastatin from nanostructured lipid carriers: physicochemical characterization and pharmacokinetics. *European Journal of Pharmaceutics and Biopharmaceutics, 74*, 474–482.

Chen, C., Han, D., Cai, C., & Tang, X. (2010). An overview of liposome lyophilization and its future potential. *Journal of Controlled Release, 142*, 299–311.

Cheong, J. N., Tan, C. P., Man, Y. B. C., & Misran, M. (2008). α-Tocopherol nanodispersions: preparation, characterization and stability evaluation. *Journal of Food Engineering, 89*, 204–209.

Cho, E. C., Lim, H. J., Kim, H. J., Son, E. D., Choi, H. J., Park, J. H., et al. (2009). Role of pH-sensitive polymer-liposome complex in enhancing cellular uptake of biologically active drugs. *Materials Science and Engineering: C, 29*, 774–778.

Chonn, A., & Cullis, P. R. (1998). Recent advances in liposome technologies and their applications for systemic gene delivery. *Advanced Drug Delivery Reviews, 30*, 73–83.

Colas, J. S., Shi, W., Malleswara Rao, V. S. N., Omri, A., Mozafari, M. R., & Singh, H. (2007). Microscopical investigations of nisin-loaded nanoliposomes prepared by Mozafari method and their bacterial targeting. *Micron, 38*, 841–847.

Constantinides, P. P., Chaubal, M. V., & Shorr, R. (2008). Advances in lipid nanodispersions for parenteral drug delivery and targeting. *Advanced Drug Delivery Reviews, 60*.

Crowe, L. M., Womersley, C., Crowe, J. H., Reid, D., Appel, L., & Rudolph, A. (1986). Prevention of fusion and leakage in freeze-dried liposomes by carbohydrates. *Biochimica et Biophysica Acta (BBA) - Biomembranes, 861*, 131–140.

Cruz, L., Soares, L. U., Costa, T. D., Mezzalira, G., da Silveira, N. P., Guterres, S. S., et al. (2006). Diffusion and mathematical modeling of release profiles from nanocarriers. *International Journal of Pharmaceutics, 313*, 198–205.

Dufour, P., Laloy, E., Vuillemard, J. C., & Simard, R. (1996). Liposomes in cheesemaking. In D. Lasic, & Y. Barenholz (Eds.), *Handbook of nonmedical applications of liposomes*. Boca Raton: CRC Press.

Fang, J.-Y., Fang, C.-L., Liu, C.-H., & Su, Y.-H. (2008). Lipid nanoparticles as vehicles for topical psoralen delivery: Solid lipid nanoparticles (SLN) versus nanostructured lipid carriers (NLC). *European Journal of Pharmaceutics and Biopharmaceutics, 70*, 633–640.

Fang, Z., & Bhandari, B. (2010). Encapsulation of polyphenols - a review. *Trends in Food Science & Technology, 21*, 510–523.

Farokhzad, O. C., & Langer, R. (2009). Impact of nanotechnology on drug delivery. *ACS Nano, 3*, 16–20.

Fathi, M., & Mohebbi, M. (2010). Increasing food safety using nanotechnology. *Magazine of Nanotechnology Initative Council, 143*, 16–18.

Freitas, C., & Müller, R. H. (1998). Spray-drying of solid lipid nanoparticles (SLN). *European Journal of Pharmaceutics and Biopharmaceutics, 46*, 145–151.

Gallarate, M., Trotta, M., Battaglia, L., & Chirio, D. (2009). Preparation of solid lipid nanoparticles from W/O/W emulsions: preliminary studies on insulin encapsulation. *Journal of Microencapsulation: Micro and Nano Carriers, 26*, 394–402.

Ghosh, A., Mandal, A. K., Sarkar, S., Panda, S., & Das, N. (2009). Nanoencapsulation of quercetin enhances its dietary efficacy in combating arsenic-induced oxidative damage in liver and brain of rats. *Life Sciences, 84*, 75–80.

Gibbs, B. F., Kermasha, S., Alli, I., & Mulligan, C. N. (1999). Encapsulation in the food industry: a review. *International Journal of Food Science and Nutrition, 50*, 213–224.

Gonnet, M., Lethuaut, L., & Boury, F. (2010). New trends in encapsulation of liposoluble vitamins. *Journal of Controlled Release*. doi:10.1016/j.jconrel.2010.1001.1037.

Goyal, P., Goyal, K., Kumar, S. G. Y., Singh, A., Ktare, O. P., & Mishra, D. N. (2005). Liposomal drug delivery systems – clinical applications. *Acta pharmaceutica, 55*, 1–25.

Gregoriadis, G. (1993). Liposome preparation and related techniques. In G. Gregoriadis (Ed.), *Liposome technology, Vol. 1* (pp. 1–63). Boca Raton: CRC Press.

Gregoriadis, G. (2007). *Liposome technology*. In: *Liposome preparation and related techniques, Vol. I*. Healthcare: Informa.

Guo, H., Wilking, J. N., Liang, D., Mason, T. G., Harden, J. L., & Leheny, R. L. (2007). Slow, nondiffusive dynamics in concentrated nanoemulsions. *Phsical Review E, 75*, 1–8.

Gutieırrez, J. M., Gonzaılez, M., Solè, I., Pey, C. M., & Nolla, J. (2008). Nano-emulsions: new applications and optimization of their preparation. *Current Opinion in Colloid & Interface Science, 13*, 245–251.

Haidar, Z. S., Hamdy, R. C., & Tabrizian, T. (2008). Protein release kinetics for coreeshell hybrid nanoparticles based on the layer-by-layer assembly of alginate and chitosan on liposomes. *Biomaterials, 29*, 1207–1215.

Hamouda, T., & Baker Jr., J. R. (2000). Antimicrobial mechanism of action of surfactant lipid preparations in enteric Gram-negative bacilli. *Journal of Applied Microbiology, 89*, 397–403.

Hamouda, T., Myc, A., Donovan, B., Shih, A. Y., Reuter, J. D., & Baker Jr., J. R. (2001). A novel surfactant nanoemulsion with a unique non-irritant topical antimicrobial activity against bacteria, enveloped viruses and fungi. *Microbiological Research, 156*, 1–7.

Hauser, H., & Strauss, G. (1988). Stabilization of small, unilamellar phospholipid vesicles by sucrose during freezing and dehydration. *Advances in Experimental Medicine And Biology, 238*, 71–80.

Hayashi, H., Kono, K., & Takagishi, T. (1996). Temperature-controlled release property of phospholipid vesicles bearing a thermo-sensitive polymer. *Biochimica et Biophysica Acta (BBA) - Biomembranes, 1280*, 127–134.

Heikal, A., Box, K., Rothnie, A., Storm, J., Callaghan, R., & Allen, M. (2009). The stabilisation of purified, reconstituted P-glycoprotein by freeze drying with disaccharides. *Cryobiology, 58*, 37–44.

Helgason, T., Awad, T. S., Kristbergsson, K., McClements, D. J., & Weiss, J. (2009a). Effect of surfactant surface coverage on formation of solid lipid nanoparticles (SLN). *Journal of Colloid and Interface Science, 334*, 75–81.

Helgason, T., Awad, T. S., Kristbergsson, K., McClements, D. J., & Weiss, J. (2009b). Influence of polymorphic transformations on gelation of tripalmitin solid lipid nanoparticle suspensions. *Journal of American Oil Chemistry Society, 85*, 501–511.

Henry, J. V. L., Fryer, P. J., Frith, W. J., & Norton, I. T. (2010). The influence of phospholipids and food proteins on the size and stability of model sub-micron emulsions. *Food Hydrocolloids, 24*, 66–71.

Hentschel, A., Gramdorf, S., Müller, R. H., & Kurz, T. (2008). β-Carotene-loaded nanostructured lipid carriers. *Journal of Food Science, 73*, N1–N6.

Higuchi, T. (1963). Mechanism of sustained-action medication: theoretical analysis of rate of release of solid drugs dispersed in solid matrices. *Journal of Pharmaceutical Sciences, 52*, 1145–1149.

Huwiler, A., Kolter, T., Pfeilschifter, J., & Sandhoff, K. (2000). Physiology and pathophysiology of sphingolipid metabolism and signaling. *Biochimica ET Biophysica Acta, 1485*, 63–99.

Iwanaga, K., Ono, S., Narioka, K., Kakemi, M., Morimoto, K., Yamashita, S., et al. (1999). Application of surface-coated liposomes for oral delivery of peptide: effect of coating the liposome's surface on the GI transit of insulin. *Journal of Pharmaceutical Sciences, 88*, 248–252.

Jafari, S. M., Assadpoor, E., Bhandari, B., & He, Y. (2008). Nano-particle encapsulation of fish oil by spray drying. *Food Research International, 41*, 172–183.

Jafari, S. M., He, Y., & Bhandari, B. (2006). Nano-emulsion production by sonication and microfluidization - a comparison. *International Journal of Food Properties*, *9*, 475–485.

Jaiswal, J., Gupta, S. K., & Kreuter, J. (2004). Preparation of biodegradable cyclosporinenanoparticles by high-pressure emulsification-solvent evaporation process. *Journal of Controlled Release*, *96*, 169–178.

Jalsenjak, I. (1992). In vitro release from microcapsules and microspheres. In M. Donbrow (Ed.), *Microcapsules and nanoparticles in medicine and pharmacy* (pp. 193–218). Boca Raton: CRC Press.

Jee, J.-P., Lim, S.-J., Park, J.-S., & Kim, C.-K. (2006). Stabilization of all-trans retinol by loading lipophilic antioxidants in solid lipid nanoparticles. *European Journal of Pharmaceutics and Biopharmaceutics*, *63*, 134–139.

Jenning, V., Schäfer-Korting, M., & Gohla, S. (2000). Vitamin A-loaded solid lipid nanoparticles for topical use: drug release properties. *Journal of Controlled Release*, *66*, 115–126.

Jesorka, A., & Orwar, O. (2008). Liposomes: technologies and analytical applications. *Annual ReviewofAnalyticalChemistry*, *1*, 801–832.

Kadimi, U. S., Balasubramanian, D. R., Ganni, U. R., Balaraman, M., & Govindarajulu, V. (2007). In vitro studies on liposomal amphotericin B obtained by supercritical carbon dioxide-mediated process. *Nanomedicine*, *3*, 273–280.

Kawai, K., & Suzuki, T. (2007). Stabilizing effect of four types of disaccharide on the enzymatic activity of freeze-dried lactate dehydrogenase: step by step evaluation from freezing to storage. *Pharmaceutical Research*, *24*, 1883–1890.

Kentish, S., Wooster, T. J., Ashokkumar, M., Balachandran, S., Mawson, R., & Simons, L. (2008). The use of ultrasonics for nanoemulsion preparation. *Innovative Food Science and Emerging Technologies*, *9*, 170–175.

Khosravi-Darani, K., Pardakhty, A., Honarpisheh, H., Rao, V. S. N. M., & Mozafari, M. R. (2007). The role of high-resolution imaging in the evaluation of nanosystems for bioactive encapsulation and targeted nanotherapy. *Micron*, *38*, 804–818.

Kirby, C. J. (1993). Controlled delivery of functional food ingredients: opportunities for liposomes in the food industry. In G. Gregoriadis (Ed.), *Liposome technology*. London: CRC Press.

Kitano, H., Maeda, Y., Takeuchi, S., Ieda, K., & Aizu, Y. (1994). Liposomes containing amphiphiles prepared by using a lipophilic chain transfer reagent: responsiveness to external stimuli. *Langmuir*, *10*, 403–406.

Klinkesorn, U., & McClements, D. J. (2009). Influence of chitosan on stability and lipase digestibility of lecithin-stabilized tuna oil-in-water emulsions. *Food Chemistry*, *114*, 1308–1315.

Kong, R., Xia, Q., & Liu, G. Y. (2011). Preparation and characterization of vitamin A palmitate-loaded nanostructured lipid carriers as delivery systems for food products. *Advanced Materials Research*, *236-238*, 1818–1823.

Kono, K., Hayashi, H., & Takagishi, T. (1994). Temperature-sensitive liposomes: liposomes bearing poly (N-isopropylacrylamide). *Journal of Controlled Release*, *30*, 69–75.

Kono, K., Nakai, R., Morimoto, K., & Takagishi, T. (1999). Thermosensitive polymer-modified liposomes that release contents around physiological temperature. *Biochimica et Biophysica Acta (BBA) - Biomembranes*, *1416*, 239–250.

Lakkis, J. M. (2007). Introduction. In J. M. Lakkis (Ed.), *Encapsulation and controlled release: Technologies in food systems* (pp. 1–12). Iowa: Blackwell Publishing.

Laye, C., McClements, D. J., & Weiss, J. (2008). Formation of biopolymer-coated liposomes by electrostatic deposition of chitosan. *Journal of Food Science*, *73*, 7–15.

Lee, S., & McClements, D. J. (2010). Fabrication of protein-stabilized nanoemulsions using a combined homogenization and amphiphilic solvent dissolution/evaporation approach. *Food Hydrocolloids*, *24*, 560–569.

Leong, T. S. H., Wooster, T. J., Kentish, S. E., & Ashokkumar, M. (2009). Minimising oil droplet size using ultrasonic emulsification. *Ultrasonics Sonochemistry*, *16*, 721–727.

Li, H., Song, J., Park, J., & Han, K. (2003). Polyethylene glycol-coated liposomes for oral delivery of recombinant human epidermal growth factor. *International Journal of Pharmaceutics*, *258*, 11–19.

Li, N., Zhuang, C., Wang, M., Sun, X., Nie, S., & Pan, W. (2009). Liposome coated with low molecular weight chitosan and its potential use in ocular drug delivery. *International Journal of Pharmaceutics*, *379*, 131–138.

Lim, S. J., & Kim, C. K. (2002). Formulation parameters determining the physicochemical characteristics of solid lipid nanoparticles loaded with all-trans retinoic acid. *International Journal of Pharmecutical*, *243*, 135–146.

Lippacher, A., Müller, R. H., & Mader, K. (2004). Liquid and semisolid SLN(TM) dispersions for topical application: rheological characterization. *European Journal of Pharmaceutics and Biopharmaceutics*, *58*, 561–567.

Lippacher, A., Müller, R. H., & Mوder, K. (2002). Semisolid SLN(TM) dispersions for topical application: influence of formulation and production parameters on viscoelastic properties. *European Journal of Pharmaceutics and Biopharmaceutics*, *53*, 155–160.

Liu, W., Sun, D., Li, C., Liu, Q., & Xu, J. (2006). Formation and stability of paraffin oil-in-water nano-emulsions prepared by the emulsion inversion point method. *Journal of Colloid and Interface Science*, *303*, 557–563.

Liu, Z., Jiao, Y., Wang, Y., Zhou, C., & Zhang, Z. (2008). Polysaccharides-based nanoparticles as drug delivery systems. *Advanced Drug Delivery Reviews*, *60*, 1650–1662.

Lo, Y. L., Tsai, J. C., & Kuo, J. H. (2004). Liposomes and disaccharides as carriers in spray-dried powder formulations of superoxide dismutase. *Journal of Controlled Release*, *94*, 259–272.

Maa, Y.-F., & Hsu, C. C. (1999). Performance of sonication and microfluidization for liquidâ€"liquid emulsification. *Pharmaceutical Development and Technology*, *4*, 233–240.

Madene, A., Jacquot, M., Scher, J., & Desobry, S. (2006). Flavour encapsulation and controlled release - a review. *International Journal of Food Science and Technology*, *41*, 1–21.

Mäder, K., & Mehnert, W. (2005). Solid Lipid nanoparticles - concepts, procedures, and physicochemical aspects. In: *Lipospheres in drug targets and delivery*. CRC Press.

Mainardes, R. M., & Evangelista, R. C. (2005). PLGA nanoparticles containing praziquantel: effect of formulation variables on size distribution. *International Journal of Pharmaceutics*, *290*, 137–144.

Malheiros, P. S., Daroit, D. J., & Brandelli, A. (2010). Food applications of liposome-encapsulated antimicrobial peptides. *Trends in Food Science & Technology*, *21*, 284–292.

Malheiros, P. S., Daroit, D. J., Silveira, N. P., & Brandelli, A. (2010). Effect of nanovesicle-encapsulated nisin on growth of Listeria monocytogenes in milk. *Food Microbiology*, *27*, 175–178.

Maruno, M., & da Rocha-Filho, P. A. (2010). O/W nanoemulsion after 15 years of preparation: a suitable vehicle for pharmaceutical and cosmetic applications. *Journal of Dispersion Science and Technology*, *31*, 17–22.

Mason, T. G., & Rai, P. K. (2003). Shear-induced elastification of concentrated emulsions probed by sinusoidal amplitude variation rheometry. *Journal of Rheology*, *47*, 513–533.

Mason, T. G., Wilking, J. N., Meleson, K., Chang, C. B., & Graves, S. M. (2006). Nanoemulsions: formation, structure, and physical properties. *Journal of Physics: Condensed Matter*, *18*, R635–R666.

Mason, T. J. (1992). Industrial sonochemistry: potential and practicality. *Ultrasonics*, *30*, 192–196.

Maulucci, G., De Spirito, M., Arcovito, G., Boffi, F., Castellano, A. C., & Briganti, G. (2005). Particle size distribution in DMPC vesicle

solutions undergoing different sonication times. *Biophysical Journal, 88*, 3545–3550.
McClements, D. J., & Li, Y. (2010). Structured emulsion-based delivery systems: controlling the digestion and release of lipophilic food components. *Advances in Colloid and Interface Science, 59*(2), 213–228.
Mehnert, W., & Mader, K. (2001). Solid lipid nanoparticles production, characterization and applications. *Advanced Drug Delivery Reviews, 47*, 165–196.
Meleson, K., Graves, S., & Mason, T. G. (2004). Formation of concentrated nanoemulsions by extreme shear. *Soft Mater, 2*, 109–123.
Mishima, K. (2008). Biodegradable particle formation for drug and gene delivery using supercritical fluid and dense gas. *Advance in Drug Delivery Reviews, 60*, 411–432.
Moran, C., Ross, J., Cunningham, C., Butler, M., Anderson, T., Newby, D., et al. (2006). Manufacture and acoustical characterisation of a highfrequency contrast agent for targeting applications. *Ultrasound in Medicine and Biology, 32*, 421–428.
Mozafari, M. R. (2005a). Liposomes: an overview of manufacturing techniques. *Cellular and Molecular Biology Letters, 10*, 711–719.
Mozafari, M. R. (2005b). Method and apparatus for producing carrier complexes. In U. Patent (Ed.), (Vol. No. GB 0404993.8).
Mozafari, M. R. (2006a). Bioactive entrapment and targeting using nanocarrier technologies: an introduction. In M. R. Mozafari (Ed.), *Nanocarrier technologies* (pp. 1–16). Netherlands: Springer.
Mozafari, M. R. (2006b). *Nanocarrier technologies: Frontiers of nanotherapy*. Dordrecht: Springer.
Mozafari, M. R. (2010). Nanoliposomes: preparation and analysis. In J. M. Walker (Ed.), *Liposomes, Vol. 605* (pp. 29–50). Humana Press.
Mozafari, M. R., Johnson, C., Hatziantoniou, S., & Demetzos, C. (2008). Nanoliposomes and their applications in food nanotechnology. *Journal of Liposome Research, 18*, 309–327.
Mozafari, M. R., & Khosravi-Darani, K. (2007). An overview of liposome-derived nanocarrier technologies. In M. R. Mozafari (Ed.), *Nanomaterials and nanosystems for biomedical applications* (pp. 113–123). Dordrecht: Springer.
Mozafari, M. R., & Mortazavi, S. M. (2005). *Nanoliposomes: from fundamentals to recent developments*. Oxford: Trafford.
Mozafari, M. R., Reed, C. J., Rostron, C., Kocum, C., & Piskin, E. (2002). Construction of stable anionic liposome-plasmid particles using the heating method: a preliminary investigation. *Cellular and Molecular Biology Letters, 7*, 923–927.
Mui, B., & Hope, M. J. (2007). Formation of large unilamellar vesicles by extrusion. In G. Gregoriadis (Ed.), *Liposome technology. Liposome preparation and related techniques, Vol. I*. Healthcare: Informa.
Müller, R. H., Dingler, A., Schneppe, T., & Gohla, S. (2000). Large-scale production of solid lipid nanoparticles (SLN) and nanosuspensions. In D. L. Wise (Ed.), *Handbook of pharmaceutical controlled release technology* (pp. 377–392). New York: CRC Press.
Müller, R. H., Lippacher, A., & Gohla, S. (2000). Solid lipid nanoparticles (SLN) as a carrier system for the controlled release of drugs. In D. L. Wise (Ed.), *Handbook of pharmaceutical controlled release technology* (pp. 377–392). New York: CRC Press.
Müller, R. H., Mader, K., & Gohla, S. (2000). Solid lipid nanoparticles (SLN) for controlled drug delivery - a review of the state of the art. *European Journal of Pharmaceutics and Biopharmaceutics, 50*, 161–s177.
Müller, R. H., Petersen, R. D., Hommoss, A., & Pardeike, J. (2007). Nanostructured lipid carriers (NLC) in cosmetic dermal products. *Advanced Drug Delivery Reviews, 59*, 522–530.
Müller, R. H., Radtke, M., & Wissing, S. A. (2002a). Nanostructured lipid matrices for improved microencapsulation of drugs. *International Journal of Pharmaceutics, 242*, 121–128.
Müller, R. H., Radtke, M., & Wissing, S. A. (2002b). Solid lipid nanoparticles (SLN) and nanostructured lipid carriers (NLC) in cosmetic and dermatological preparations. *Advanced Drug Delivery Reviews, 54*, 131–155.
Müller, R. H., & Runge, S. A. (1998). Solid lipid nanoparticles (SLN) for controlled drug delivery. In S. Benita (Ed.), *Submicron emulsions in drug targeting and delivery*. Amsterdam: Harwood Academic Publishers.
Müllers, R. H., Schwarz, C., Mehnert, W., & Lucks, J. S. (1993). Production of solid lipid nanoparticles (SLN) for controlled drug delivery. *Proceeding of International Symposium Controlled Release Bioactive Materials, 20*, 480–481.
zur Mühlen, A., Schwarz, C., & Mehnert, W. (1998). Solid lipid nanoparticles (SLN) for controlled drug delivery - drug release and release mechanism. *European Journal of Pharmaceutics and Biopharmaceutics, 45*, 149–155.
Nagle, J. F., & Tristram-Nagle, S. (2000). Structure of lipid bilayers. *Biochimica et Biophysica Acta (BBA) - Reviews on Biomembranes, 1469*, 159–195.
Neethirajan, S., & Jayas, D. (2010). Nanotechnology for the Food and Bioprocessing Industries. *Food and Bioprocess Technology*, 1–9.
Padamwar, M. N., & Pokharkar, V. B. (2006). Development of vitamin loaded topical liposomal formulation using factorial design approach: drug deposition and stability. *International Journal of Pharmaceutics, 320*, 37–44.
Parasassi, T., Di Stefano, M., Loiero, M., Ravagnan, G., & Gratton, E. (1994). Influence of cholesterol on phospholipid bilayers phase domains as detected by Laurdan fluorescence. *Biophysical Journal, 66*, 120–132.
Patel, G. B., & Chen, W. (2006). Archaeosomes as drug and daccine danodelivery systems. In M. R. Mozafari (Ed.), *Nanocarrier technologies* (pp. 17–40). Netherlands: Springer.
Patil, M. N., & Pandit, A. B. (2007). Cavitation - a novel technique for making stable nano-suspensions. *Ultrasonics Sonochemistry, 14*, 519–530.
Pereira-Lachataignerais, J., Pons, R., Panizza, P., Courbin, L., Rouch, J., & Lopez, O. (2006). Study and formation of vesicle systems with low polydispersity index by ultrasound method. *Chemistry and Physics of Lipids, 140*, 88–97.
Pinnamaneni, S., Das, N. G., & Das, S. K. (2003). Comparison of oil-in-water emulsions manufactured by microfluidization and homogenization. *Pharmazie, 58*, 554–558.
Porras, M., Solans, C., GonzJlez, C., & Gutiérrez, J. M. (2008). Properties of water-in-oil (W/O) nano-emulsions prepared by a low-energy emulsification method. *Colloids and Surfaces A: Physicochemical and Engineering Aspects, 324*, 181–188.
Quintanilla-Carvajal, M., Camacho-Díaz, B., Meraz-Torres, L., Chanona-Pérez, J., Alamilla-Beltrán, L., Jimenéz-Aparicio, A., et al. (2010). Nanoencapsulation: a new trend in food engineering processing. *Food Engineering Reviews, 2*, 39–50.
Radtke, M., & Müller, R. H. (2001). NLS™ nanostructured lipid carriers: the new generation of lipid drug carriers. *New Drugs, 2*, 48–52.
Rao, D. R., Chawan, C. B., & Veeramachaneni, R. (1995). Liposomal encapsulation of beta-galactosidase - comparison of two methods of encapsulation and in vitro lactose digestibility. *Journal of Food Biochemistry, 18*, 239–251.
Rizvi, S. S. H., Moraru, C. I., Bouwmeester, H., & Kampers, F. W. H. (2010). Nanotechnology and food safety. In E. B. Christine, S. Aleksandra, O. Sangsuk, & L. M. L. Huub (Eds.), *Ensuring global food safety* (pp. 263–280). San Diego: Academic Press.
Rossi, J., & Leroux, J. C. (2007). Principles in the development of intravenous lipid emulsions. In K. Wasan (Ed.), *Role of lipid excipients in modifying oral and parenteral drug delivery* (pp. 88–123). New Jersey: Wiley-Interscience.
Russel, W. B., Saville, D. A., & Schowalter, W. R. (1989). *Colloidal dispersions*. Cambridge University Press.

Sagalowicz, L., Leser, M. E., Watzke, H. J., & Michel, M. (2006). Monoglyceride self-assembly structures as delivery vehicles. *Trends in Food Science & Technology*, *17*, 204–214.

Sahin, N. O. (2007). Niosomes as nanocarrier systems. In M. R. Mozafari (Ed.), *Nanomaterials and nanosystems for biomedical applications* (pp. 67–81). Netherlands: Springer.

Sakulku, U., Nuchuchua, O., Uawongyart, N., Puttipipatkhachorn, S., Soottitantawat, A., & Ruktanonchai, U. (2009). Characterization and mosquito repellent activity of citronella oil nanoemulsion. *International Journal of Pharmaceutics*, *372*, 105–111.

Samer, C. J., & Schork, F. (1999). The role of high shear in continuous miniemulsion polymerization. *Industrial & Engineering Chemistry Fundamentals*, *38*, 1801–1807.

Samuni, A., Lipman, A., & Barenholz, Y. (2000). Damage to liposomal lipids: protection by antioxidants and cholesterol-mediated dehydration. *Chemistry and Physics of Lipids*, *105*, 121–134.

Sanguansri, P., & Augustin, M. A. (2006). Nanoscale materials development - a food industry perspective. *Trends in Food Science & Technology*, *17*, 547–556.

Sant, S., Nadeau, V., & Hildgen, P. (2005). Effect of porosity on the release kinetics of propafenone-loaded PEG-g-PLA nanoparticles. *Journal of Controlled Release*, *107*, 203–214.

Saupe, A., & Rades, T. (2006). Solid lipid nanoparticles. In M. R. Mozafari (Ed.), *Nanocarrier technologies: Frontiers of nanotherapy* (pp. 41–50). Dordrecht: Springer.

Schäfer-Korting, M., & Mehnert, W. (2005). Delivery of lipophilic compounds with lipid nanoparticles - applications in dermatics and for transdermal therapy. In: *Lipospheres in drug targets and delivery*. CRC Press.

Schroeder, A., Kost, J., & Barenholz, Y. (2009). Ultrasound, liposomes, and drug delivery: principles for using ultrasound to control the release of drugs from liposomes. *Chemistry and Physics of Lipids*, *162*, 1–16.

Schwarz, C., & Mehnert, W. (1997). Freeze-drying of drug-free and drug-loaded solid lipid nanoparicles. *International Journal of Pharmaceutics*, *157*, 171–179.

Shah, R. B., Zidan, A. S., Funck, T., Tawakkul, M. A., Nguyenpho, A., & Khan, M. A. (2007). Quality by design: characterization of self-nano-emulsified drug delivery systems (SNEDDs) using ultrasonic resonator technology. *International Journal of Pharmaceutics*, *341*, 189–194.

Shakeel, F., & Ramadan, W. (2010). Transdermal delivery of anticancer drug caffeine from water-in-oil nanoemulsions. *Colloids and Surfaces B: Biointerfaces*, *75*, 356–362.

Sharma, A., & Sharma, U. S. (1997). Liposomes in drug delivery: progress and limitations. *International Journal of Pharmaceutics*, *154*, 123–140.

Shimoni, E. (2009). Nanotechnology for foods: delivery systems. In B.-C. Gustavo, M. Alan, L. David, S. Walter, B. Ken, & C. Paul (Eds.), *Global issues in food science and technology* (pp. 411–424). San Diego: Academic Press.

Siepmann, J., Faisant, N., & Benoit, J.-P. (2002). A new mathematical model quantifying drug release from bioerodible microparticles using monte carlo simulations. *Pharmaceutical Research*, *19*, 1885–1893.

Solans, C., Esquena, J., Forgiarini, A., Uson, N., Morales, D., Izquierdo, P., et al. (2003). Absorption and aggregation of surfactants in solution. In K. L. Mittal, & O. S. Dinesh (Eds.), *Nano-emulsions: Formation, properties and applications* (pp. 525–554). New York: Marcel Dekker.

Sudimack, J. J., Guo, W., Tjarks, W., & Lee, R. J. (2002). A novel pH-sensitive liposome formulation containing oleyl alcohol. *Biochimica et Biophysica Acta (BBA) - Biomembranes*, *1564*, 31–37.

Suntres, Z. E., & Shek, P. N. (1996). Alleviation of paraquat-induced lung injury by pre-treatment with bifunctional liposomes containing alpha-tocopherol and glutathione. *Biochemical Pharmacology*, *52*, 1515–1520.

Tadros, T., Izquierdo, P., Esquena, J., & Solans, C. (2004). Formation and stability of nano-emulsions. *Advances in Colloid and Interface Science*, *108–109*, 303–318.

Talegaonkar, S., Mustafa, G., Akhter, S., & Iqbal, Z. I. (2010). Design and development of oral oil-in-water nanoemulsion formulation bearing atorvastatin: in vitro assessment. *Journal of Dispersion Science and Technology*, *31*, 690–701.

Taylor, T. M., Bruce, B. D., Weiss, J., & Davidson, P. M. (2008). Listeria monocytogenes and Escherichia coli O157:H7 inhibition in vitro by liposome-encapsulated nisin and ethylene diaminetetraacetic acid. *Journal of Food Safety*, *28*, 183–197.

Taylor, T. M., Davidson, P. M., Bruce, B. D., & Weiss, J. (2005a). Liposomal nanocapsules in food science and agriculture. *Critical Reviews in Food Science and Nutrition*, *45*, 587–605.

Taylor, T. M., Davidson, P. M., Bruce, B. D., & Weiss, J. (2005b). Ultrasonic spectroscopy and differential scanning calorimetry of liposomal-encapsulated nisin. *Journal of Agricultural and Food Chemistry*, *53*, 8722–8728.

Taylor, T. M., Gaysinsky, S., Davidson, P. M., Bruce, B. D., & Weiss, J. (2007). Characterization of antimicrobial-bearing liposomes by ζ-potential, vesicle size, and encapsulation efficiency. *Food Biophysics*, *2*, 1–9.

Teeranachaideekul, V., Müller, R. H., & Junyaprasert, V. B. (2007). Encapsulation of ascorbyl palmitate in nanostructured lipid carriers (NLC)—Effects of formulation parameters on physicochemical stability. *International Journal of Pharmaceutics*, *340*, 198–206.

Teixeira, P. C., Leite, G. M., Domingues, R. G., Silva, J., Gibbs, P. A., & Ferreira, J. P. (2007). Antimicrobial effects of a microemulsion and a nanoemulsion on enteric and other pathogens and biofilms. *International Journal of Food Microbiology*, *118*, 15–19.

Thompson, A. K., Hindmarsh, J. P., Haisman, D., Rades, T., & Singh, H. (2006). Comparison of the structure and properties of liposomes prepared from milk fat globule membrane and soy phospholipids. *Journal of Agriculture and Food Chemistry*, *54*, 3704–3711.

Unger, E. C., Porter, T., Culp, W., Labell, R., Matsunaga, T., & Zutshi, R. (2004). Therapeutic applications of lipid-coated microbubbles. *Advanced Drug Delivery Reviews*, *56*, 1291–1314.

Varshosaz, J., Ghaffari, S., Khoshayand, M. R., Atyabi, F., Azarmi, S., & Kobarfard, F. (2010). Development and optimization of solid lipid nanoparticles of amikacin by central composite design. *Journal of Liposome Research*, *20*, 97–104.

Varshosaz, J., Minayian, M., & Moazen, E. (2010). Enhancement of oral bioavailability of pentoxifylline by solid lipid nanoparticles. *Journal of Liposome Research*, *20*, 115–123.

Varshosaz, J., Tabbakhian, M., & Mohammadi, M. Y. (2009). Formulation and optimization of solid lipid nanoparticles of buspirone HCl for enhancement of its oral bioavailability. *Journal of Liposome Research*1–11.

Wajda, R. (2003). Emulsive water soluble concentrates. In (Vol. Patent.WO2004/047791 A2).

Wajda, R., Zirkel, J., & Schaffer, T. (2007). Increase of bioavailability of coenzyme Q(10) and vitamin E. *Journal of Medicinal Food*, *10*, 731–734.

Washington, C. (1998). Drug release and interfacial structure in emulsions. In R. H. Miller, S. Benita, & B. Böhm (Eds.), *Emulsions and nanosuspensions for the formulation of poorly soluble drugs*. Stuttgart: Medpharm.

Watwe, R. M., & Bellare, J. R. (1995). Manufacture of liposomes: a review. *Current Science*, *68*, 715–724.

Weiss, J., Decker, E. A., McClements, D. J., Kristbergsson, K., Helgason, T., & Awad, T. (2008). Solid lipid nanoparticles as

delivery systems for bioactive food components. *Food Biophysics, 3*, 146–154.

Weiss, J., Gaysinsky, S., Davidson, M., & McClements, J. (2009). Nanostructured encapsulation systems: food antimicrobials. In B.-C. Gustavo, M. Alan, L. David, S. Walter, B. Ken, & C. Paul (Eds.), *Global issues in food science and technology* (pp. 425–479). San Diego: Academic Press.

Were, L. M., Bruce, B., Davidson, P. M., & Weiss, J. (2004). Encapsulation of nisin and lysozyme in liposomes enhances efficacy against Listeria monocytogenes. *Journal of Food Protection, 67*, 922–927.

Were, L. M., Bruce, B. D., Davidson, P. M., & Weiss, J. (2003). Size, stability, and entrapment efficiency of phospholipid nanocapsules containing polypeptide antimicrobials. *Journal of Agricultural and Food Chemistry, 51*, 8073–8079.

Westesen, K., Bunjes, H., & Koch, M. H. J. (1997). Physicochemical characterisation of lipid nanoparticles and evaluation of their drug loading capacity and sustained release potential. *Journal of Controlled Release, 48*, 223–236.

Westesen, K., Siekmann, B., & Koch, M. H. J. (1993). Investigations on the physical state of lipid nanoparticles by synchrotron radiation X-ray diffraction. *International Journal of Pharmecutical, 93*, 189–199.

Wissing, S. A., & Müller, R. H. (2002). Solid lipid nanoparticles as carrier for sunscreens: in vitro release and in vivo skin penetration. *Journal of Controlled Release, 81*, 225–233.

Wulff-Perez, M., Torcello-Gomez, A., Galvez-Ruız, M. J., & Martın-Rodrıguez, A. (2009). Stability of emulsions for parenteral feeding: Preparation and characterization of o/w nanoemulsions with natural oils and Pluronic f68 as surfactant. *Food Hydrocolloids, 23*, 1096–1102.

Yang, S., & Washington, C. (2006). Drug release from microparticulate systems. In S. Benita (Ed.), *Microencapsulation: Methods and industrial applications*. Boca Raton: CRC Press.

Ye, Q., Asherman, J., Stevenson, M., Brownson, E., & Katre, N. V. (2000). DepoFoam™ technology: a vehicle for controlled delivery of protein and peptide drugs. *Journal of Controlled Release, 64*, 155–166.

Yuan, Y., Gao, Y., Mao, L., & Zhao, J. (2008). Optimisation of conditions for the preparation of β-carotene nanoemulsions using response surface methodology. *Food Chemistry, 107*, 1300–1306.

Yung, B., Shek, P. N., & Stanacev, N. Z. (1985). Topological distribution of bovine serum albumin in multilamellar and unilamellar liposomes. *Chemistry and Physics of Lipids, 37*, 283–295.

Yurdugul, S., & Mozafari, M. R. (2004). Recent advances in micro- and nano-encapsulation of food ingredients. *Cellular and Molecular Biology Letters, 9*, 64–65.

Zaru, M., Manca, M. L., Fadda, A. M., & Antimisiaris, S. G. (2009). Chitosan-coated liposomes for delivery to lungs by nebulisation. *Colloids and Surfaces B: Biointerfaces, 71*, 88–95.

Zasadzinski, J. A. (1986). Transmission electron microscopy observations of sonication-induced changes in liposome structure. *Biophysical Journal, 49*, 1119–1130.

Zhang, M., Yang, Z., Chow, L. L., & Wang, C. H. (2003). Simulation of drug release from biodegradable polymeric microspheres with bulk and surface erosions. *Journal of Pharmaceutical Sciences, 92*, 2040–2056.

Zhuang, C.-Y., Li, N., Wang, M., Zhang, X.-N., Pan, W.-S., Peng, J.-J., et al. (2010). Preparation and characterization of vinpocetine loaded nanostructured lipid carriers (NLC) for improved oral bioavailability. *International Journal of Pharmaceutics, 394*, 179–185.

Zimet, P., & Livney, Y. D. (2009). Beta-lactoglobulin and its nanocomplexes with pectin as vehicles for ω-3 polyunsaturated fatty acids. *Food Hydrocolloids, 23*, 1120–1126.

Zignani, M., Drummond, D. C., Meyer, O., Hong, K., & Leroux, J.-C. (2000). In vitro characterization of a novel polymeric-based pH-sensitive liposome system. *Biochimica et Biophysica Acta (BBA) - Biomembranes, 1463*, 383–394.

Zimmermann, E., & Müller, R. H. (2001). Electrolyte- and pH-stabilities of a queous solid lipid nanoparticle (SLN™) dispersions in artificial gastrointestinal media. *European Journal of Pharmaceutics and Biopharmaceutics, 52*, 203–210.