Chapter 5
Nanoencapsulation Technologies

Yoav D. Livney

Abstract Technologies for nanoencapsulation of nutraceuticals for the enrichment of food and beverages are being developed and studied intensively, and are gradually becoming implemented by the food industry. The advances in research evidencing the health benefits of nutraceuticals, on the one hand, and the controllable risks involved in food nanotechnology on the other, have led to growing public acceptance. Consumers seek health-promoting foods that would not compromise sensory quality, or be more expensive, and comprise only natural, label-friendly ingredients. The collected knowledge and improved technological abilities generate an exciting plethora of innovative nanostructured delivery systems for nutraceuticals (e.g. nanostructured lipid carriers, nanoliposomes, co-assembled protein nanoparticles and nanofibers, and mixed polysaccharide-surfactant nanovehicles). These are formed using various novel encapsulation technologies, based on top-down, bottom-up or combined approaches. The novel nanovehicles facilitate solubilization and protection through processing, shelf life and digestion. Moreover, such nanovehicles enable programmed release and improved bioavailability of nutraceuticals, resulting in enhanced beneficial health effects.

5.1 Introduction

Over the last few decades, there is growing public awareness of the strong linkage between food and health, based on a rapidly growing body of scientific literature. As the world faces serious noncommunicable diseases, such as cardiovascular diseases, obesity, diabetes and cancer, the fast progress in food nanotechnology carries great promise to provide new and effective functional foods as tools for preventing and possibly even curing to some of these global illnesses.

Y.D. Livney (✉)
Faculty of Biotechnology and Food Engineering, Russell Berrie Nanotechnology Institute, Technion—Israel Institute of Technology, 3200000 Haifa, Israel
e-mail: livney@technion.ac.il

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The exciting nanostructure of raw and processed food is gradually being revealed thanks to progress in nanoscopic imaging and other physico-chemical characterization techniques. This facilitates advancement in our understanding of food structure and properties, and in our ability to control and manipulate food nanostructure and to create novel and better food functionalities.

As with any revolutionary new technology, along with its great promise, food nanotechnology raises some concerns. These concerns of possible toxicity due to the much higher penetrability of nanoparticles (NPs) through biological barriers seem to have hampered progress and implementation. However, the prudent approach taken by regulators, researchers, and manufacturers, and the rising awareness of the potential benefits of these technologies, seem to be paving the way for their safe and extensive application, and for wide public acceptance.

This chapter focuses on structure and production technologies of nanodelivery systems for health-promoting bioactive compounds (nutraceuticals) in functional foods, an important and fast developing field in food nanotechnology. Most nutraceuticals cannot be incorporated in foods or beverages in their pure form. This may be attributed either to poor solubility, sensitivity to degradation during processing, shelf life and digestion, undesired sensory attributes, or poor bioavailability, and often a combination of a few of these reasons. These limitations hinder the applicability and diminish efficacy of these compounds in preventing diseases. Nanodelivery systems are designed to overcome these obstacles. Nevertheless, to be applicable and commercially viable, these delivery systems must be safe for consumption, cost effective, available on demand, simple and convenient to use, upscalable and robust, label-friendly (particularly for certain consumer groups, e.g. those with allergies, vegetarians, certain religions), and they must not adversely affect the sensory properties of the enriched product. Enhanced bioavailability, and negligible undesired sensory impact are the main advantages of nanodelivery systems.

The chapter reviews selected recently published papers in order to highlight the latest progress and to envisage potential trends for future advances.

5.2 Classification of Food Nanodelivery Systems

Numerous types of nanodelivery systems have been reported and reviewed in the literature (Cerqueira et al. 2014; Yao et al. 2014, 2015; Norton et al. 2015; Walker et al. 2015). Those studied and developed over the past 2–5 years include nanoemulsions, nanostructured lipid carriers (NLCs), Pickering emulsions, solid lipid NPs (SLN), nanosuspensions, liposomes and nanoliposomes, NPs and micelles made of proteins, polysaccharides and their complexes or conjugates, and combinations with lipid or mineral components.

Nanoemulsions (Fig. 5.1a) are colloidal dispersions of small liquid droplets, <100 nm (Gulotta et al. 2014; Walker et al. 2015). They may be oil-in-water (O/W) or water-in-oil (W/O), or even bicontinuous, and either liquid in liquid or liquid in

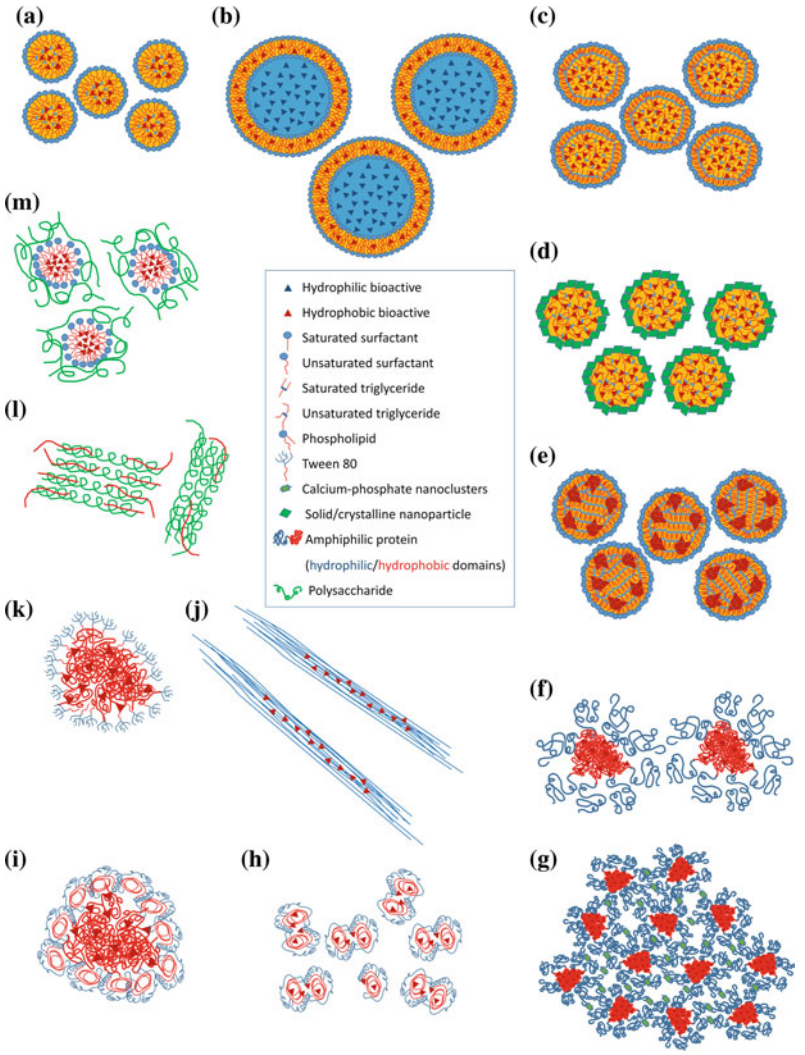

Fig. 5.1 Types of nanostructured delivery systems studied recently. **a** Nanoemulsion (liquid core, droplet size <100 nm, often <50 nm). **b** Liposomes (~200 nm to several microns) and nanoliposomes (<200 nm) (unilamellar depicted, carrying both hydrophilic and hydrophobic bioactives). **c** Nanostructured lipid carriers (NLCs) (e.g. liquid core, and crystalline shell; size <100 nm). **d** Pickering emulsion: liquid core stabilized by adsorbed solid nanoparticles. **e** Solid–lipid NPs (SLN) (a lipid nanosuspension, or a nanoemulsion with solidified droplets and bioactive; typical size <100 nm). **f** Amphiphilic biopolymer (e.g. casein) Nps (typical size <100 nm). **g** Reassembled casein micelle (size range 50–500 nm). **h** Protein-bioactive nanocomplexes (e.g. β-lactoglobulin-naringenin; size range 5–50 nm). **i** Hydrophobic protein (e.g. Zein) encapsulated by an amphiphilic one (e.g. β-lactoglobulin; size range 100–1000 nm). **j** Electrospun protein nanofibres (~500 nm thick). **k** Hydrophobic protein (e.g. Zein, ~80 nm nanoaggregate) encapsulated by a surfactant (e.g. Tween 80, ~4 nm thick nanocoat). **l** Amylose inclusion complexes entrapping fatty acids (internal structure is nanometric; particles are micrometric). **m** Polysaccharide-lipid NPs (e.g. Quercetin encapsulated in lecithin/chitosan NPs, 150–190 nm)

solid (the latter may be called solid emulsions—e.g. butter, a W/O solid emulsion). The interface may be stabilized by various types of emulsifiers, whose structure and amphiphilicity determine droplet curvature and size. Also the oil type and composition, the surfactant-to-oil ratio, and the presence of cosolvents and cosolutes may affect droplet size and emulsion stability (Komaiko and McClements 2015). The main types of amphiphiles used for nanoemulsion formation include low molecular weight surfactants, either synthetic surfactants like Tween 80 (Cho et al. 2014; Gulotta et al. 2014), Tween 20 (Salvia-Trujillo et al. 2013), and sucrose palmitate (Rao et al. 2013), or natural surfactants such as phospholipids (Lane et al. 2014) and saponins (Yang and McClements 2013); high molecular weight biopolymeric amphiphiles (Livney 2012), either synthetic like octenyl succinate modified starch (Hategekimana et al. 2014), or natural, like milk proteins (Livney 2010), particularly caseins (Penalva et al. 2015), whey proteins, mainly β-lactoglobulin (Pool et al. 2013), and milk protein peptides (Adjonu et al. 2014). Nanoemulsions are usually made either by high-shear/high-energy homogenization methods, or by low-energy, spontaneous self-emulsification methods (Piorkowski and McClements 2014; Komaiko and McClements 2015).

Liposomes (Fig. 5.1b), or vesicles, are typically spherical liquid structures with an aqueous core surrounded by a single (unilamellar) or several lipid bilayer(s) (multilamellar liposomes). Liposomes smaller than 200 nm are sometimes referred to as nanoliposomes. The main advantage of liposomes is their ability to deliver both hydrophilic and lipophilic bioactive compounds, even simultaneously. Another advantage is their similarity to natural cell membranes. However, they are quite sensitive to shear and environmental stresses, such as osmotic pressure differences, and their production scale-up is challenging. Liposomes were recently studied for their performance in the delivery of carotenoids (Tan et al. 2014), which exhibited different loading abilities into liposomes: lutein > β-carotene > lycopene > canthaxanthin. A similar trend was found for their antioxidant activity against lipid peroxidation during preparation (Tan et al. 2014). Green tea catechins, which are water-soluble bioactives, have also been encapsulated in liposomes (Rashidinejad et al. 2014). The liposomes were made of soy lecithin, and were ∼130 nm before loading, but significantly increased in size upon catechin incorporation. Loading efficiency was >70 %. The liposomes were added to the milk during low-fat hard cheese production, and almost no catechins were lost in the whey (Rashidinejad et al. 2014). Coencapsulation of lipophilic and hydrophilic nutraceuticals in unilamellar soy phospholipid-based nanoliposomes was studied using two types of commercial plant sterols—water- and oil-soluble—as well as their effect on the stability and encapsulation efficiency of ascorbic acid, a hydrophilic nutraceutical. Liposomes were prepared using high-pressure homogenization at pH 7. All liposomes obtained showed an initial monomodal size distribution with an average diameter of 115–150 nm. Incorporation of plant sterols increased the vesicle size and their encapsulation efficiency. Dilution showed content release over time (Alexander et al. 2012). Niosomes are liposomes made of nonionic surfactants. Niosomes made of a food-grade synthetic surfactant, sorbitan monostearate (Span 60), with lauryl alcohol (dodecanol) for membrane stabilization have been used for entrapping resveratrol for yogurt enrichment (Pando et al. 2015).

Nanostructured lipid carriers (NLCs) (Fig. 5.1c) are partially crystallized lipid nanovehicle particles with mean size of ≤ 100 nm, dispersed in an aqueous phase containing emulsifier(s) (Tamjidi et al. 2013). The partially solid material creates interesting nanostructures that enhance stability of entrapped bioactives, enable high loading capacity, and offer sustained-release profiles. In one study, different antioxidants (EDTA, ascorbic acid, α-tocopherol, coenzyme Q_{10}) were added to aqueous and/or lipid phases in order to observe the effect on the physical and chemical stability of NLCs (stabilized by Tween 80 and lecithin) containing astaxanthin, a hydrophobic nutraceutical. Small NPs ($\sim$94 nm) were obtained for all formulations except those with high levels of EDTA or ascorbic acid, and were stable to growth during storage at 35 °C for 15 days. EDTA and α-tocopherol increased astaxanthin oxidative stability while maintaining physical stability, with EDTA showing greater efficiency (Tamjidi et al. 2014). The influence of surfactant properties [low (LM)- and high-melting (HM) lecithins] on the physical and chemical stability of NLCs containing tristearin and omega-3 fish oil was investigated (Salminen et al. 2013), and the presence of fish oil was found to reduce the crystallization temperature, melting temperature, and melting enthalpy of tristearin. NLCs stabilized with HM-lecithin inhibited the oxidation of omega-3 fatty acids ≥ 90 % compared to those stabilized with LM-lecithin. This was attributed to the solidified surfactant layer of HM-lecithin inducing crystallization of the shell by interfacial heterogeneous nucleation (Salminen et al. 2013). Another interesting type of NLC is Pickering emulsions (Fig. 5.1d), where solid NPs are adsorbed, sometimes sintered, to the oil–water interface and provide much higher stability to emulsions than is obtainable with surfactant molecules (Dickinson 2012; Norton et al. 2015).

Nanosuspensions are systems in which solid NPs, stabilized by amphiphiles, are dispersed in a liquid medium. An interesting type of nanosuspension are solid lipid NPs (SLNs) (Fig. 5.1e), which are typically made of nanoemulsions whose dispersed phase has later been fully crystallized, and is composed of a solid carrier lipid–bioactive ingredient mixture (Salminen et al. 2013). Protein-stabilized SLNs have also been reported. One study investigated NPs containing β-carotene (BC), and encapsulated by either sodium caseinate (SC) or whey protein isolates (WPI). The BC-loaded NPs with 0.75 % SC and 1.0 % WPI were 75 and 90 nm in diameter, respectively. Sizes increased by less than 10 % at 4 °C, but by 10−76 % at 25 °C over 30 days of storage. The oxidative stability of BC was higher in SC than in WPI, and the chemical stability of BC increased as protein concentration increased (Yi et al. 2014). To enhance the apparent solubility of quercetin, three types of transglycosylated materials were studied: α-glycosyl hesperidin (Hsp-G), α-glycosyl stevia (Stevia-G) and α-glycosyl rutin (Rutin-G). The solubilizing effect of these amphiphiles decreased as follows: Rutin-G > Hsp-G > Stevia-G. The apparent solubility of quercetin from the spray-dried sample with Rutin-G was 43-fold higher than that of the quercetin crystal, likely due to the formation of molecular-level quercetin/Rutin-G nanostructured composite particles in aqueous media (Fujimori et al. 2015).

Protein/peptide nanovehicles: Curcumin was encapsulated in casein NPs (Fig. 5.1f) by spray drying their aqueous ethanol solution, which inhibited curcumin crystallinity, and obtained apparent aqueous solubility four orders of magnitude higher than with pristine curcumin (Pan et al. 2013). Curcumin was also encapsulated in native-like

phosphocasein micelles, which were improved by ultrahigh-pressure homogenization (Benzaria et al. 2013). Reassembled casein micelles (Fig. 5.1g) have been recently applied for encapsulation of β-carotene (Saiz-Abajo et al. 2013). Fish or vegetable oils have been encapsulated in casein micelles using combinations of pH modification and sonication (Ghasemi and Abbasi 2014). Whey proteins have also been studied intensively as nanovehicles for nutraceuticals. We recently formed β-Lg-naringenin nanocomplexes (Fig. 5.1h), which suppressed naringenin crystallization, for increasing its effective solubility and promoting its bioavailability (Shpigelman et al. 2014). The application of whey protein aggregation for nanocoating production was recently reviewed (Ramos et al. 2014). Lactoferrin (LF) has been studied as a vehicle for (-)-epigallocatechin-3-gallate (EGCG). Interestingly, EGCG exhibited a strong affinity for native LF, but a weak affinity for thermally modified LF at pH 5.0 and 6.5, and an inverse result at pH 3.5 (Yang et al. 2014b). Whey protein hydrolyzates were used for nanoencapsulation of caffeine, by transglutaminase cross-linking and desolvation by ethanol. Interestingly, the protective antioxidative activity of the peptides was enhanced by the transglutaminase cross-linking (Bagheri et al. 2014). Whey protein hydrolysate has also been used to chelate calcium, and the WPH-calcium chelate demonstrated excellent stability (Xixi et al. 2015). Calcium delivery by peptides was also tackled from a more unique approach, using carp egg-phosphopeptide. In vitro, egg-phosphopeptide exhibited high Ca binding ability, which was slightly lower than that of casein-phosphopeptide and could inhibit the formation of insoluble Ca salts (Huang et al. 2014). Our group recently reported employing soybean β-conglycinin (β-CG) NPs to encapsulate vitamin D (VD), thereby protecting it from thermal degradation and during shelf life (Levinson et al. 2014). Barley protein NPs (90–150 nm) have been studied as an oral delivery system for lipophilic bioactives, using high-pressure homogenization, and without organic solvents, surfactants or cross-linking agents. The NPs exhibited good colloidal stability and high loading capacity (~50 %) (Yang et al. 2014a). Omega-3-rich fish oil was encapsulated in zein via alcohol evaporation. Oil-free and fish oil-loaded zein NPs were 69 and 83 nm on average, respectively. They were added into a sugar beet pectin (SBP) solution that was subsequently gelified by the enzyme laccase (Soltani and Madadlou 2015). Tangeretin, a hydrophobic flavonoid, was encapsulated in protein NPs produced by mixing an organic phase containing zein and tangeretin with an aqueous phase containing β-lactoglobulin (Fig. 5.1i) (Chen et al. 2014).

Not only NPs, but also nanofibers made of protein have been studied as possible nanovehicles for bioactives. Electrospun zein nanofibers (~500 nm thick) loaded with fish oil were prepared (Fig. 5.1j). The lipid phase tended to concentrate at the core of the fibers, which provide a greater oxidative stability compared to non-encapsulated fish oil (Moomand and Lim 2014). Gallic acid was also incorporated into electrospun zein nanofibers (330–390 nm) as a functional ingredient. Gallic acid had retained its antioxidant activity after incorporation in the nanofibers (Neo et al. 2013).

Protein–surfactant NPs: Zein–Tween 80 NPs (Fig. 5.1k) were proposed as food-grade delivery systems. The NPs had a zein core of 78 nm diameter and a Tween 80 shell with a thickness around 4 nm (Hu and McClements 2014).

Polysaccharide-based NPs: Enzymatically synthesized dextran NPs (100–450 nm) were developed for entrapping hydrophobic nutraceuticals. Dextransucrase generated spherical dextran NPs from sucrose, which were later loaded with genistein and freeze dried (Semyonov et al. 2014). High amylose corn starch (HACS) (Fig. 5.1l) was used for encapsulating omega-3 fatty acids or silymarin for enriching bread as a functional food. Improved thermal stability of the heat labile bioactives during baking was reported (Mogol et al. 2013). Sodium alginate was used to encapsulate folic acid, using electrohydrodynamic technology to generate fine droplets (micrometers to nanometers in diameter) cross-linked in $CaCl_2$ solution (Bakhshi et al. 2013).
Polysaccharide-lipid NPs: Quercetin was encapsulated into lecithin/chitosan NPs ($\sim$170 nm) (Fig. 5.1m). Encapsulated quercetin showed improved antioxidant properties compared to free quercetin (Souza et al. 2014).

5.3 Nanoencapsulation Technologies

There are many different nanoencapsulation techniques, nanocapsule structures, and encapsulation materials, and the choice of the most suitable technology (materials, structure and technique) should be based on several considerations, including:

1. The properties of the bioactive to be encapsulated (e.g. hydrophobicity, charge), and of the intended product(s) for enrichment (e.g. water/oil-based continuous phase, liquid/solid).
2. The purpose of encapsulation, e.g. solubilization, protection (from heat, oxidizing agents, extreme pH, enzymes, etc.) during processing, shelf life, digestion; masking of undesired taste or odor; controlled release during digestion and/or facilitation of bioavailability.
3. Safety and efficacy of the technology in the intended final product(s) and any regulatory constraint.
4. Special requirements of the intended consumers [e.g. allergies, nutritional preferences like vegetarians/vegans, religious constraints (Kosher, Halal, etc.), preference for natural ingredients, etc.].
5. Intellectual property (IP) rights.
6. Availability of resources (skilled workers, equipment, materials).
7. Cost-effectiveness.

Nanoencapsulation Approaches
The process design, equipment and conditions should be chosen according to the materials used (bioactive and encapsulating materials) and the required structure, properties and physical state (e.g. liquid/powder etc.) of the desired nanocapsules. In general, the physicochemical properties such as particle size, size distribution, surface area, shape, solubility, encapsulation efficiency, and release mechanisms may be modified by the encapsulation technique (Ezhilarasi et al. 2013;

McClements 2015). Nanoencapsulation technologies may be divided into "top-down" and "bottom-up" approaches, wherein the particle size is respectively reduced or increased during the process of NP formation; however, combined approaches (McClements 2015) are also available. A top-down approach applies tools that allow size reduction and structure shaping for the desired application of the nanomaterials being developed (Ezhilarasi et al. 2013). Most top-down methods are based on mechanical forces. The major unit operations applied for mechanical size reduction are shearing/homogenization, grinding, injection/extrusion and spraying (McClements 2015). Bottom-up techniques are mostly based on physicochemical processes. The bottom-up approach is more common in nanoencapsulation, as it is generally simpler and requires less energy to form colloidally stable nano-sized particles via spontaneous self-assembly or co-assembly of molecules, than by breaking down larger structures. Bottom-up, self-assembly-based processes are, however, highly dependent on solution conditions such as temperature, pH, ionic strength etc. (Augustin and Sanguansri 2009). As an example, nanoemulsions may be produced by either a top-down or a bottom-up approach. Top-down emulsification techniques use high energy, to exert high shear on oil–water-surfactant mixtures or primary emulsions, e.g. using various homogenizers, to disrupt oil–water interface and effect droplet breakdown and size reduction down to the desired nanoscale (Abbas et al. 2013; Komaiko and McClements 2015). In contrast, bottom-up approaches for nanoemulsification require no special equipment and rely on the properties of the surfactant, oil, and water system, utilizing low energy processes, like simple mixing procedures or by changing system conditions such as temperature, to induce spontaneous formation of nanodroplets by surfactant self-assembly (Solans and Solé 2012; Schalbart and Kawaji 2013; Komaiko and McClements 2015). Combined approaches embody methods wherein some of the components are down-sized, while others are assembled, or where initial steps encompass size reduction, and later stages include nanocoating of the particles formed by co-assembly with dissolved coating materials, e.g. in layer-by-layer deposition of polyelectrolytes around emulsion droplets (Ogawa et al. 2004; McClements et al. 2009).

Another important aspect is the control of the state and internal structure of the core material. High melting point bioactives and carrier lipids tend to crystallize at storage temperature (which is an advantage for stability, but a disadvantage for bioavailability). Careful temperature control during particle formation, (e.g. heating before homogenization, and cooling afterwards) may enable the formation of solid lipid nanoparticles (SLNs) (Muller et al. 2000; Weiss et al. 2008; Aditya et al. 2014; Pandita et al. 2014; Yi et al. 2014) or partially solid, nanostructured lipid carriers (NLCs) (Tamjidi et al. 2013; Zheng et al. 2013; Aditya et al. 2014). Pickering emulsions, in which solid particles adsorb to the oil–water interface providing superb stability, may be formed by adding solid nanoparticles to either the aqueous or the oil phase (Ghouchi Eskandar et al. 2007) prior to adding the oil phase and emulsifying, but to form O/W Pickering emulsions, the solid nanoparticles should be better wetted by the aqueous phase (Dickinson 2010).

Top-Down Approaches: Reduction of Particle/Droplet Size

Size reduction may be achieved predominantly by mechanical means, which require significant energy input to overcome cohesive energy holding the molecules together in solid or liquid states, and to create larger surface area, which entails high surface energy.

(i) **High-shear/homogenization**

High shear/homogenization methods are designed and used widely for processing liquid dispersions/emulsions of various types (McClements 2015), making particle sizes smaller and more uniform. Some of the instruments used are also useful for combining and blending different streams, which is also very useful for nanoencapsulation, enabling combined top down and bottom up processes. Following are the main types of high shear/homogenization instruments useful for nanoencapsulation:

High-shear mixers are widely used to form coarse emulsions (2–10 μ) (Walstra 1993; McClements 2015), as a preliminary step before high-pressure homogenization. They are also useful for making colloidal dispersions, e.g. from phase-separated biopolymer mixtures like water-in-water (W/W) emulsions or oil-in-water-in-water (O/W/W) systems (Matalanis et al. 2010; McClements 2015). These high-shear mixers usually comprise a high-speed spinning mixing head and a container that may range in volume from a few cubic centimeters (lab scale) to several cubic meters (industrial scale) (McClements 2015). Various mixing head designs are available for different needs (Walstra 1993; McClements 2015).

High-pressure valve homogenizers (HPVHs) are perhaps the most widely used homogenizers for decreasing emulsion droplet size (McClements 2005; Lee et al. 2013), forming more uniform emulsions, and often follow a high shear mixer (McClements 2015). An HPVH usually has a piston-based pump that draws the coarse emulsion and forces it through a controllable-gap valve, where shear, cavitation, impact and turbulence break down the droplets (McClements 2005, 2015; Lee et al. 2013). Surface tension, surfactants used, and ratio of viscosities of the dispersed and continuous phases affect final droplet size distribution (Wooster et al. 2008; Lee et al. 2013). Increasing homogenization pressure, surfactant concentration and number of passes generally decrease resulting droplet size (Qian and McClements 2011). Often, a second stage of lower pressure-drop follows immediately to dissociate "flocs" formed after the first stage. HPVHs are most suitable for low to medium viscosities, and it is possible to obtain emulsion droplets <500 nm, and even <100 nm if several passes are used and a proper surfactant at sufficient concentration is present to cover the droplets (Wooster et al. 2008; McClements 2015).

Ultrasonic homogenizers harness high intensity and frequency sound waves (fluctuating pressure) to disrupt droplets and particles thus reducing their size, mainly by cavitation and microturbulence (Walstra 1993; Jafari et al. 2007; Kentish et al. 2008; McClements 2015). The two most common types are ultrasonic probe

and ultrasonic jet homogenizers (McClements 2015). The former is usually for batch, while the latter is mainly for continuous processes (Kentish et al. 2008; McClements 2015). Droplet size decreases with increasing intensity and duration of sonication, while the efficiency decreases with increasing viscosity of the phases (Jafari et al. 2007; Kentish et al. 2008; McClements 2015). Temperature rise is a problem in this technique; hence, sonication is often applied in a series of short bursts (McClements 2015).

Microfluidizers are ultrahigh-pressure homogenizers with unique flow path designs which either split the flow in two jets and then collide them head on (McClements 2005, 2015), or form a jet via an orifice, and direct it into through a reactor chamber, colliding it with a "dead-end" so that it reverses around the incoming jet, causing a counter-flow shear (Semo et al. 2007; Alvarez-Sabatel et al. 2015), thereby forming extremely fine droplets or nano-sized particles. The size obtained, which may be <100 nm, depends on the flow design, the pressure, the number of passes, and on the composition (mainly type and concentration of emulsifier used) (Wooster et al. 2008; Qian and McClements 2011). Microfluidizers are suitable for low to intermediate viscosity fluids (McClements 2015). Beyond emulsions, microfluidizers may be used for other types of colloidal systems, such as biopolymer-based systems (Panagiotou et al. 2008), and in certain instruments, it is possible to combine two streams just before homogenization, which is very useful for entrapping bioactives in nanocarrier material (Semo et al. 2007), for example, by antisolvent-induced precipitation methods, or to form a microemulsion without the need to form a coarse pre-emulsion (McClements 2015).

Microchannel homogenizers are still used mainly in research due to challenging scale-up. They are useful for creating uniform-sized and well-defined internally structured emulsions, by directing two or more streams via geometrically precise microchannels—for example, concentric channels forming core–shell microcapsular or nanocapsular structures. Droplets as small as 300 nm may be formed (Nisisako 2008; Neethirajan et al. 2011; Vladisavljević et al. 2012; McClements 2015).

Membrane homogenizers are also mainly used for research, due to the difficulties in scale-up. They are useful for creating very uniform droplets even directly from separate oil and water flows, or for reducing droplet size of a coarse pre-emulsion (Nazir et al. 2010; McClements 2015). The emulsion is formed by forcing the eventual discontinuous phase through a rigid membrane of uniform pore size into the continuous immiscible phase, which usually contains an emulsifier. The droplet size depends on the pore size, the emulsifier type and concentration, the pressure drop across the membrane, and the flow profile of the continuous phase (McClements 2015). Membrane (and also microchannel) homogenizers may also be used to form other types of colloidal particles, besides emulsions. For example, hydrogel beads may be formed by preparing a W/O pre-emulsion containing a gelling agent in the water phase, passing it through the membrane to reduce droplet size, then changing the conditions to induce gelation in the micro/nanodroplets (Zhou et al. 2008; McClements 2015).

(ii) **Spraying/atomization**
Spraying and atomization usually refer to the formation of droplets by forcing a liquid to break and disperse into fine droplets in a gas phase (Peltonen et al. 2010).

Spray drying has for many years been one of the most widely used industrial methods for drying liquids into powders and for encapsulation of active ingredients (Vega and Roos 2006; Paudel et al. 2013; McClements 2015). The principle of spray drying used for encapsulation is pumping a solution or dispersion of the active compound containing the wall material, usually in the continuous phase, through an atomizer (e.g. a nozzle, a vibrating mesh (Lee et al. 2011), an ultrasonic nozzle (Semyonov et al. 2011) or a spinning disk), which converts the liquid into a fine mist sprayed into a drying chamber, where hot air usually flows (co-current or counter-current with respect to the falling droplets), evaporating the solvent (usually water) from the droplets, and thereby converting them into small powder particles (typically 10–1000 μ). A novel Nano Spray Dryer equipped with a vibrating mesh spray technology and an electrostatic particle collector was reported to form spherical BSA NPs of about 460 nm in diameter (Lee et al. 2011). The powder is separated from the gas by gravity, filtration or centrifugally by cyclones (Vega and Roos 2006; Paudel et al. 2013; McClements 2015). Further processing may be also performed, e.g. coating or agglomeration (Fang and Bhandari 2012). There are several advantages to converting a liquid form of an active material into a powdered solid form: storage stability increases thanks to the solid state and the protective wall material, as well as improvement of handling and utilization properties, and reduced storage and shipping costs. Spray drying in particular is a rather mild drying process, which can be used for encapsulating heat-sensitive materials [particularly when done under low pressure, which may even enable survival of probiotic bacteria (Semyonov et al. 2011)], because the droplet temperature rise is suppressed by the latent heat of evaporation until solidification (Fang and Bhandari 2012; McClements 2015).

Spray chilling uses similar equipment to spray drying, but sprays a hot liquid (like molten fat) into a cold chamber to induce droplet solidification (Gamboa et al. 2011; Oxley 2012b; McClements 2015). This method is useful for encapsulation with lipids whose melting points range ~30–70 °C. The encapsulated compound is first dispersed or dissolved in the lipid carrier above its melting temperature. Chilling temperature must be sufficiently lower than the melting point to assure sufficient supercooling to initiate nucleation and crystallization (McClements 2015). Spray chilling may also be used for creating microgel or nanogel particles based on cold-setting polymers (Oxley 2012b). Spray chillers are often combined with fluidized bed coolers for a second stage cooling, and additional agglomeration or coating is also possible (McClements 2015).

Electrospraying utilizes electrical voltage to accelerate the sprayed droplets from the nozzle to a collecting electrode-plate, thereby helping to break them into much smaller droplets, which rapidly dry by evaporation before reaching the collecting plate. Particle size may be controlled by adjusting flow rate, applied voltage, and solution composition (Jaworek 2008; McClements 2015).

(iii) **Milling**
Breaking down bulk solid matrices may be a useful step in the formation of certain colloidal delivery systems. This may be achieved by several mechanical milling devices (Hu et al. 2004; Peltonen and Hirvonen 2010; Muller et al. 2011; McClements 2015). Milling may be done on dry bulk or powdered solids, or on solid in liquid dispersions. Mechanical milling devices, depending on design, exert shear, attrition, compression, or impact forces and their combinations, to reduce particle size, and they vary in the type and amount/capacity of processable materials, minimal particle size obtainable, equipment and operating costs, etc. (McClements 2015). Examples of milling devices include hammer mills, ball mills, pearl (bead) mills, cylindrical roll mills, and colloid mills (Muller et al. 2011; Bolenz and Manske 2013; Burmeister and Kwade 2013; McClements 2015).

Colloid mills are useful for dispersions of solids or liquids in viscous liquids systems (Walstra 1993; McClements 2005, 2015). They are typically made of a rotor and a stator with a gap between them that becomes narrower with the direction of flow. Usually a coarse emulsion is fed in, as they are inefficient in blending separate oil and water phases (McClements 2015). As with homogenization, a surface stabilizer or emulsifier is usually needed during milling to stabilize the newly formed surfaces and prevent aggregation (McClements 2015).

(iv) **Extrusion**
Extrusion, in the production of microparticles or NPs, encompasses the injection of a liquid through one or more thin nozzles to form small droplets, and then to fix/solidify and/or encapsulate them to form stable particles (Hu et al. 2004; Oxley 2012a; McClements 2015). For example, a solution of a polymer (possibly containing emulsion droplets of a bioactive) may be extruded into a solidifying solution, e.g. calcium ions for physical cross-linking of alginate, glutaraldehyde for chemical cross-linking of a protein, or transglutaminase for enzymatic cross-linking of a protein, or by cooling, e.g. to induce agar gelation, or to induce molten lipid crystallization (Hu et al. 2004; Oxley 2012a; McClements 2015). Co-extrusion of the core and the coating in a concentric extrusion device may be used as an elegant way to form capsular structures, and simultaneous extrusion through numerous parallel extrusion nozzles may facilitate scale-up (Oxley 2012a). Microfluidic devices may facilitate versatile formation of particles of well-defined dimensions and internal structure (Helgeson et al. 2011; Desmarais et al. 2012; McClements 2015).

(v) **Coating**
Top-down coating may be applied to confer protection, to shield and separate the core materials from the surroundings or from possible reactants, to mask undesirable flavors/odors of the core, or to control the digestive release and the

bioavailability of the coated bioactives. Some (bottom-up) coating is obtained spontaneously during particle formation—e.g. when surfactants are present during homogenization or milling. Coextrusion, mentioned above, is generally a top-down coating method. Spray coating is another top-down coating technique, in which a coating liquid (a solution, a suspension or a hot melt) is sprayed onto particles, which are usually suspended by air flow in a fluidized bed set-up, followed by hardening of the coating by drying or cooling. This method is quite limited to microencapsulation, as the core particle size is in the range of 50–500 μ (Gibbs 1999; Oxley 2012b; McClements 2015).

(vi) **Bottom-Up Approaches**
Various bottom-up approaches for nanoencapsulation have been developed over the last few decades. These techniques harness fundamental understanding of physical chemistry, to induce self-assembly and co-assembly of molecules by manipulating intermolecular forces and entropic effects by selecting molecules of desired structures and properties, and by carefully controlling the composition (bioactives, encapsulation materials and solvents), the order of mixing and the process conditions (pH, ionic strength, temperature, pressure, mixing turbulence, etc.).

- **Bottom-up emulsification methods**

Spontaneous emulsification (SE): E.g. titrating a mix of oil and a water-soluble surfactant into an aqueous solution (water + cosolvent, like ethanol) while stirring (Saberi et al. 2013; McClements 2015).
Emulsion inversion point (EIP): E.g. titrating water into a mixture of oil and a water-soluble surfactant while stirring. First, a W/O emulsion is formed, then an O/W/O, then a W/O emulsion (Ostertag et al. 2012; McClements 2015).
Phase inversion temperature (PIT): E.g. a mixture of a nonionic surfactant, oil and water is heated to just above its PIT, and then is quench-cooled while stirring, to form a nanoemulsion (Anton and Vandamme 2009; McClements 2015). Above the PIT the surfactant is more soluble in the oil phase, and forms a curvature favorable for W/O emulsion. At the PIT curvature is 0, and further cooling results in O/W as the surfactant head becomes more hydrophilic. In all the three methods above, lipophilic bioactives are added initially into the oil-phase (McClements 2015).

- **Bottom-up polymeric NP formation**
Polymer-based NPs may be formed by a variety of methods, and the appropriate polymer(s) and formation method should be chosen based on the properties of the bioactive to be encapsulated (solubility, charge, etc.), the goals of encapsulation (e.g. solubilization, protection, taste masking), the properties of the considered polymer(s) and the expected interaction mechanisms between the bioactive and the polymer (hydrophobic and van der Waals, electrostatic interactions, etc.).

Single polymer systems may be divided into single-molecule nanovehicles and multi-molecule NPs—for example, aggregates, micelles and nanocomplexes. Proteins that have both hydrophilic and hydrophobic domains may often serve as effective nanovehicles, particularly if they have solvent-accessible hydrophobic domains. Single molecule nanovehicles act by binding the individual bioactive molecule(s), thereby solubilizing, carrying and protecting them. For example, β-Lg (Swaisgood 2001), may serve as a unimolecular vehicle (also capable of forming dimers (Kontopidis et al. 2004), tetramers and octamers (Gottschalk et al. 2003) binding one to three molecules (Kontopidis et al. 2004) of a hydrophobic bioactive, such as vitamin D (Wang et al. 1997), DHA (Zimet and Livney 2009), or naringenin (Shpigelman et al. 2014) (Fig. 5.1h). Their formation may be achieved by dissolving the hydrophobic bioactive in a water-miscible cosolvent, such as ethanol, and slowly adding it at a predetermined proportion into the polymer solution while stirring it intensively (Zimet and Livney 2009; Shpigelman et al. 2014). The concentrations of the protein and the bioactive, and the ratio between them determines whether unimolecular or multimolecular NPs would form, and the loading efficiency and capacity obtained (David et al. 2014).

More common are the various multimolecular NPs, including various nanoaggregates and co-assemblies (Israeli-Lev and Livney 2014), micelles (Fig. 5.1f, g) (Semo et al. 2007; Bargarum et al. 2009; Zimet et al. 2011; Haham et al. 2012) and nanocomplexes (Fig. 5.1h) (Shpigelman et al. 2012; David et al. 2014). A unique strategy is exemplified by reassembled casein micelles (Fig. 5.1f) (Semo et al. 2007; Zimet et al. 2011; Haham et al. 2012), which are formed from one or several types of phosphoserine containing caseins: First the hydrophobic bioactive, predissolved in an organic water-miscible solvent, like ethanol, is added into the casein solution while stirring. Then, phosphate, citrate and lastly calcium solutions are added while stirring, to simulate the original mineral composition of milk, thereby inducing reformation of casein micelles, by bridging and clustering together the initially formed protein-bioactive coassemblies (or sub-micelles), to form the reassembled casein micelles, loaded with the bioactive (Semo et al. 2007; Zimet et al. 2011; Haham et al. 2012).

The formation of most multimolecular NPs is usually by phase separation, which may be achieved using several different approaches, aimed at controlling the solubility of the polymer and the bioactive by changing solvent composition, pH, ionic strength temperature etc. to induce the co-assembly of the polymer and the bioactive from their initially soluble forms. One of the most effective approaches is the antisolvent approach and its variations. In one such approach, the polymer is initially dissolved in a good solvent, or a neutral solvent (McClements 2015). This solution is then titrated while stirring into a bad solvent (typically containing the bioactive) to induce polymer aggregation and co-assembly with the bioactive. Possibly, for a hydrophobic polymer such as zein, it can be dissolved in an organic solvent, like ethanol, together with the hydrophobic bioactive. In this case, when

adding water as the antisolvent, it should contain an amphiphile such as Tween (Hu and McClements 2014) (Fig. 5.1k), or an amphiphilic protein (Chen et al. 2014) (Fig. 5.1i), to nanocoat the zein-bioactive nanoparticles formed upon the addition of antisolvent. Alternatively, a co-solvent containing the bioactive is titrated into the polymer solution while stirring. In this case, the bioactive starts aggregating upon the cosolvent dissipation in the polymer solution, and the polymer adsorbs onto the bioactive nanoparticles formed, entrapping them, and suppressing their further aggregation and crystallization (Shapira et al. 2012).

Mixed polymer systems comprise more than one polymer, and open a plethora of possibilities for creating nanodelivery systems. When two different polymers are mixed in solution, several main scenarios are possible, depending on the interactions between them (Grinberg and Tolstoguzov 1997; Tolstoguzov et al. 1997): in the case of repulsive interactions, at low concentrations they would be co-soluble, while at high concentrations, the system would phase separate due to thermodynamic incompatibility (Grinberg and Tolstoguzov 1997), forming two phases—each rich in one of the polymers, possibly forming a water in water (W/W) emulsion, which may be applied to form delivery systems, particularly if the dispersed phase (Matalanis and McClements 2012, 2013) or the continuous phase (or both) (Norton and Frith 2001) is/are later cross-linked for enhanced stability. In the case of attractive interactions (Tolstoguzov et al. 1997; Tolstoguzov 2002, 2006) (e.g. when the polymers are oppositely charged and ionic strength is low) at low polymer concentrations, or when one of the polymers is in considerable excess, soluble complexes are formed, which may serve as bioactive nanodelivery systems (Zimet and Livney 2009; Ron et al. 2010). When mutually attracted polymers exist at higher concentrations, and at pH and ratios under which they neutralize each other's charges, they form aggregative phase-separated systems, with a polymer rich phase and a polymer poor phase. These may either be coacervates (reversible, polymer and solvent rich) or precipitates (polymer-rich, solvent-poor, practically irreversible aggregates formed when pH, ionic strength and ratio cause very high attraction) (Tolstoguzov et al. 1997; Tolstoguzov 2002, 2006; McClements 2015). Attractive interactions may be used to form multi-layer emulsions, via layer-by-layer deposition of oppositely charged polymers on charged emulsion droplets (Bertrand et al. 2000; Caruso 2001; Ogawa et al. 2004; Klinkesorn et al. 2005; Johnston et al. 2006; McClements 2015), which is an elegant technology for protecting, delivering and controlling the release of oil-soluble bioactives. More complex systems, like microclusters (Dickinson 2012) of heteroaggregated emulsion droplets (Mao and McClements 2013), and colloidosomes (Gu et al. 2007), may be formed from emulsion droplets covered with oppositely charged polymers, which are then mixed together (McClements 2015).

Supercritical fluid technologies: A supercritical fluid is a material held pressurized above its critical temperature, so that it has liquid-like density, but low viscosity and high solubilization capacity (Cocero et al. 2009). Supercritical fluid technologies

are unique bottom-up methods which harness the ability of supercritical fluids, such as supercritical CO_2, to dissolve various compounds, then induce nanoparticle formation and simultaneous solvent removal by reducing the pressure (Cocero et al. 2009). Colloidal delivery systems may be formed in several ways, using supercritical fluids as either solvent or antisolvent (Cocero et al. 2009; McClements 2015). For example, the bioactive and the coating material may be both dissolved in the supercritical fluid, and when the solution is sprayed into a low pressure chamber, both bioactive and capsule material come out of solution and spontaneously co-aggregate into solid nanoparticles in a powder form (Cocero et al. 2009; McClements 2015). Alternatively, the active ingredient and the carrier material are first dissolved in a conventional solvent, and the solution is then brought into contact with a supercritical fluid, causing co-precipitation of the core and carrier materials. This approach may also be used to form core-shell particles by depositing the shell material onto existing core nanoparticles or nanodroplets (Cocero et al. 2009; McClements 2015).

5.4 Sensory Aspects of Nanostructured Delivery Systems in Food

Perhaps the main benefit of nanodelivery systems in food is the fact that they usually evade our sensory perception, enabling enrichment of food and beverages with bioactives without compromising the sensory attributes of the original product. Due to their nanometric size, they are too small for the naked eye, but if kept below about 80 nm (and not at very high concentrations, or particle refractive index not very different from that of the solution), they barely scatter any visible light, thus maintaining transparency. Such stealth nanovehicles are valuable, e.g. for enriching clear beverages with water-insoluble bioactives, or ones of undesirable flavors or odors. SLNs, and protein complexes were reported to mask bitterness of hesperetin (Fathi et al. 2013) and EGCG (Shpigelman et al. 2012), respectively. Nanovehicles useful for transparent beverage enrichment include, for example, nanoemulsions (Gulotta et al. 2014; Piorkowski and McClements 2014), protein NPs (Levinson et al. 2014; Shpigelman et al. 2014) and protein-polysaccharide conjugates (Markman and Livney 2012). Also, mouth-feel characteristics of NPs are nonexistent, as our tongue cannot sense particulates below $\sim$10 microns. Niosomes containing resveratrol did not cause any changes in the texture of regular yogurt (Pando et al. 2015). Nanocomplexes of high amylose corn starch encapsulating omega-3 fatty acids and silymarin were incorporated into bread formulation, and up to 2.5 % had no undesirable impact on bread quality parameters and sensory attributes (Mogol et al. 2013).

5.5 Bioavailability of Bioactives in NPs

The facilitation of micronutrient bioavailability is another major advantage of NPs. This is mainly due to their nanometric size (Cerqueira et al. 2014; Oehlke et al. 2014; Ting et al. 2014; Yao et al. 2014, 2015; Norton et al. 2015). The improved oral bioavailability is obtained by several mechanisms: increasing bioactive stability during digestion; enhancing nutraceutical solubility in intestinal fluids; enhancing nutraceutical transport and absorption through or between the intestinal epithelial cells; and decreasing first-pass metabolism in the gut and liver (Oehlke et al. 2014; Ting et al. 2014; Yao et al. 2015). The materials and their physical state, the nanostructure of the vehicles and surrounding food matrix affect bioavailability. An in vitro bioaccessibility study showed that casein NPs acted as gastroresistant devices and released folic acid only under simulated intestinal conditions (Penalva et al. 2015). β-Carotene bioaccessibility in starch hydrogels containing no fat was very low ($\sim$1 %) due to its crystallinity and lack of mixed micelles to solubilize it (Mun et al. 2015). The bioaccessibility of β-carotene increased with increasing digestible oil content (Rao et al. 2013). The bioaccessibility of quercetin in nanoemulsions was higher than in either bulk oil or pure water (Pool et al. 2013). Transglutaminase cross-linking slowed down the release rate of entrapped caffeine from sub-micron particles in a simulated gastric fluid (Bagheri et al. 2014).

The absorption of calcium from whey protein hydrolysate-calcium chelate in Caco-2 cells was significantly higher than those of calcium gluconate and $CaCl_2$ (Xixi et al. 2015). β-carotene cellular uptake was significantly improved through NP delivery systems by 2.6-, 3.4-, and 1.7-fold increase, respectively, for sodium-caseinate, whey protein, and soy-protein NPs, compared to free β-carotene (Yi et al. 2014).

The oral bioavailability of folic acid when administered to rats as casein NPs was around 52 %, which was 50 % higher than from pure solution (Penalva et al. 2015). Calcium bioavailability was significantly increased in calcium-deficient rats by egg-phosphopeptide supplementation (Huang et al. 2014). Another rat study showed that the bioavailability of heptadecanoic acid and of coenzyme Q_{10} was highest when encapsulated within digestible oil droplets of smallest size (Cho et al. 2014).

In a clinical human study, we have found that bioavailability of vitamin D_3 encapsulated in reformed-casein micelles in 1 % fat milk was at least as high as in aqueous Tween 80-emulsified vitamin D_3 supplement (Haham et al. 2012). Another clinical trial demonstrated significantly higher absorption of omega-3 fatty acids from a nanoemulsion than from bulk oil (Lane et al. 2014).

5.6 Health Aspects of NP Enrichment of Food: Safety and Efficacy

The augmented bioavailability of bioactives in NPs is also an important safety concern, particularly when the added nutraceutical or the nanovehicle material may become toxic above a certain dose. This requires a prudent safety evaluation, and regulatory approval, particularly when introducing new materials that have no record of safe human consumption. Increased bioavailability in nanovehicles may require re-evaluation of Recommended Daily Allowance (RDA) and Tolerable Upper Intake Level (UL) of bioactives.

Positive results regarding safety of food protein NPs in cell culture studies have been reported (Yu and Huang 2013; Yang et al. 2014a; Yi et al. 2014). Compared with micron-sized emulsions with the same compositions, nanoemulsions did not reveal more toxicity to Caco-2 cell monolayers (Yu and Huang 2013). Phosphocasein micelles did not induce damage or major inflammation to human intestinal epithelial TC7 cells as assessed by LDH release or IL-8 secretion (Benzaria et al. 2013).

Health-promoting attributes of nanoencapsulated bioactives are being studied extensively; however, more in vivo and clinical studies of their safety and health promotion are still needed. Casein–encapsulated curcumin showed higher antioxidant activity and higher anticancer activity, as evaluated by in vitro cell proliferation assay using human colon cancer cells, than unencapsulated curcumin (Pan et al. 2013). EGCG encapsulated in casein micelles caused a decrease in proliferation of cancer cells, while in healthy cells, neither free nor encapsulated EGCG affected cell proliferation at low concentrations, and its bioefficacy was not diminished regardless of the extent of digestion (Haratifar et al. 2014). EGCG-loaded chitosan-NPs orally administered to mice implanted with subcutaneous tumor xenografts resulted in significant tumor growth inhibition, compared with free EGCG and control groups (Khan et al. 2014). Calcium content, bone mineral density and biomechanical properties were significantly higher in rats following egg-phosphopeptide supplementation compared to control (Huang et al. 2014). Conjugated linolenic acid-rich oil nanocapsules significantly reduced the blood lipids, tissue lipids and plasma viscosity in high-fat diet induced hypercholesterolemia in rats (Sengupta et al. 2015).

Table 5.1 highlights nanoencapsulated bioactives and their nanovehicles, which were reported recently.

5.7 Potential Future Directions

Novel nanoencapsulation technologies are being introduced and developed at a fast pace, and their great potential in food is being clearly established. In light of global health problems, their utilization for effective preventive nutrition and health

Table 5.1 Nanoencapsulated bioactives reported recently

Bioactive		Nanovehicle (References)
Vitamins	D	Soybean β-conglycinin NPs (Levinson et al. 2014)
	A	Nanosuspension (Campardelli and Reverchon 2015)
	B9 (Folic acid)	Nanodroplets in calcium alginate (Bakhshi et al. 2013)
Minerals	Calcium	Whey protein hydrolysate nanocomposite (Xixi et al. 2015); carp egg phosphopeptide (Huang et al. 2014)
Carotenoids	β-Carotene	Fat droplets in starch-based filled hydrogels (Mun et al. 2015); protein-stabilized SLNs (Yi et al. 2014); nanoemulsions (Rao et al. 2013; Salvia-Trujillo et al. 2013); re-assembled casein micelles (Saiz-Abajo et al. 2013)
	Astaxanthin	NLCs (Tamjidi et al. 2014)
	Lutein, β-carotene, lycopene, canthaxanthin	Liposomes (Tan et al. 2014)
(Poly) phenols	Curcumin	Casein NPs (Pan et al. 2013); phosphocasein micelles (Benzaria et al. 2013)
	EGCG	β-Lactoglobulin complexes (Shpigelman et al. 2012); Lactoferrin-based NPs (Yang et al. 2014b); liposomes (Rashidinejad et al. 2014); chitosan-based NPs (Khan et al. 2014); casein micelles (Haratifar et al. 2014)
	Quercetin	Lecithin/chitosan NPs (Souza et al. 2014); nanoemulsion (Pool et al. 2013)
	Naringenin	β-Lactoglobulin complexes (Shpigelman et al. 2014)
	Tangeretin	Zein/β-lactoglobulin NPs (Chen et al. 2014)
	Genistein	Enzymatically synthesized dextran NPs (Semyonov et al. 2014)
	Resveratrol	Nanoemulsions (Davidov-Pardo and McClements 2014)
	Gallic acid	Electrospun zein nanofibres (Neo et al. 2013)
	Silymarin	Amylose inclusion complexes (Mogol et al. 2013)
	Hesperetin	SLNs (Fathi et al. 2013)
	Eugenol	Microemulsions (nanoemulsions) (Al-Okbi et al. 2014)
Fatty acids	Omega-3	Nanoemulsions (Salminen et al. 2013; Cho et al. 2014; Lane et al. 2014; Walker et al. 2015); SLNs (Salminen et al. 2013); NLCs (Salminen et al. 2013); zein NPs (Soltani and Madadlou 2015); casein micelles (Ghasemi and Abbasi 2014); electrospun zein fibers (Moomand and Lim 2014); amylose inclusion complexes (Mogol et al. 2013)

(continued)

Table 5.1 (continued)

Bioactive		Nanovehicle (References)
	Conjugated linolenic acid	Oil nanocapsules (microemulsions) (Sengupta et al. 2015)
Peptides	Whey protein bioactive peptides	Nanoemulsions (Adjonu et al. 2014)
Other nutraceuticals	Clove oil	Microemulsions (nanoemulsions) (Al-Okbi et al. 2014)
	Coenzyme Q_{10}	Nanoemulsions (Cho et al. 2014)

promotion is imperative and inevitable. Safety concerns must be further prudently addressed by accelerated in vivo and clinical trials to provide scientific support to both regulators and producers toward broader safe application. These studies can also provide consumers with scientific evidence-based information, contributing to the growing public acceptance of food nanotechnology (Schnettler et al. 2014), and allowing this boundless potential to be realized in numerous ways in the future. These may include personalized nutrition, delivery systems based on natural-renewable sources, novel functionalities for advancing human physical and mental competence, boosting-up mood, and raising the satisfaction from healthy food. Novel technologies like 3D printing may enable the creation of innovative functional food products, incorporating nanodelivery systems and personalizing product composition, shape and sensory attributes according to our genome and personal preferences.

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