



NANO-ENCAPSULATION APPROACH OF FOOD BIOACTIVE COMPONENTS: REVIEW

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ABSTRACT

Nano encapsulation is one of the most promising technologies for trapping bioactive compounds to prevent their destruction. Low solubility and lower absorption of bioactive compounds in the gastrointestinal limited their bioavailability. Therefore different methods for Nano encapsulation with some advantages and disadvantages were developed. One of the important benefits of this method is the deliberate release, site-specific delivery and efficient absorption of bioactive compounds through cells. Nanoparticle methods depend on a variety of factors that influence the result of the nano-protective coatings. However, researches in the application of nanotechnology in the food industry have been very limited and there are only a few review articles that explored the Nano encapsulation technology. New aspects of Nano encapsulation of food bioactive components remained unclear. This review article focuses on importance of new Nano encapsulation technologies of bioactive compounds.

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Introduction

The bioactive food components is characterized by subjecting to rapid inactivation or degradation [1-3] and many encapsulation procedures have developed to slows down the degradation processes and to protect of premature degradation until the product is delivered at the sites where adsorption is desired [4-6]. Bioactive food components can be categorized into bioactive molecules and bioactive living cells. These bioactive molecules include lipids, vitamins, peptides, fatty acids, antioxidants, minerals and also living cells such as probiotics [6-8]. Many encapsulation procedures have been proposed however, none of them is served as a gold standard for bioactive food components. Because any bioactive food components have their own characteristic molecular structure such as molecular weight, polarity, solubility, etc. [9, 10] which emphasizes that different encapsulation technics have to be applied in order to meet the specific physicochemical and molecular requirements for a specific bioactive component[9, 11].

Nanotechnology can be defined as a field of study that developed in biology, engineering, chemistry and medicine[12]. Nanotechnology focuses on matters an atomic and molecular scale. It has been generally noted nanotechnology considered to study of the structures of the dimensions between 1 and 100 nm at least one dimension and involves developing materials or devices within that size[13].

Nanotechnology is considered as an important affecting factor in many industries, including agriculture and food industry. The effect of nanotechnology on food system were observed from production to processing, storage, and development of innovative materials, products, and applications[14]. In this regard, the benefit of nanotechnology could include the

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development of nanoparticles (Nano gels, Nano capsules, etc.) for molecular encapsulation and enrichment of agrifood, control of food composition (healthy foods), specific nutraceutical delivery (e.g., vitamins, cofactor, proteins, etc.), foods for specific applications (special purpose and fortified foods), alternative noninvasive feeding (e.g., skin, mucosal), enhancement of sensorial properties (e.g., flavor, color, taste, smell, form) [14-16]. Moreover, nanotechnology can also improve the water solubility, thermal stability, and oral bioavailability of bioactive compounds [5, 13].

Many reviews and research papers have been published on the application of nanotechnology in foods [16-19] [12]; [(20)]. However, only few works were focused on Nano encapsulation of food ingredients [21] [9, 22] [23]. Therefore, the main aim of this review is to discuss the importance of bioactive food components, Nano encapsulation of bioactive food components and their advantages in health science.

Bioactive food compounds

People are increasingly trending to non-nutrient food ingredients to enriched of their meals which may play a significant role in health promotion, disease prevention and performance improvement[24, 25].

The herbal and animal sources of many bioactive food compounds derived from herbal or animal which is responsible for the positive effects on well-being[25, 26]. Several clinical and epidemiological studies during recent years have suggested there is very strong relationship between consumption of fruits and vegetables with reduce of many acute and chronic disease [4, 22, 26, 27]. It has been suggested that the main meals associated with five portions of fruits or vegetables a day could guarantee for healthy lifestyle dietary habits[28]. Many of these fruits and vegetables are sources of plant polyphenols, secondary metabolites in plants, which have health protective property such as antioxidants[29]. Both of hydrophilic and lipophilic bioactive molecules derived from various plant and animal sources may exert beneficial effects on health.

The potential health benefits of hydrophilic or lipophilic compounds, could be obtain by withstanding the various food processing, be released in enzymatic function in stomach and be available to absorb in the gastrointestinal tract, to reach the target tissue of action[30, 31]. Therefore, the bioactive compound should be bioavailable before it can have an effect. The term bioavailability is commonly referred to as the ability to use nutrients after absorption[13].

Bioavailability has a key role in understanding of health potential of foods and food components, followed by knowledge of the circulating metabolites, which leads to understanding of the mechanisms of action in relation to the benefit[2, 13].

Due to the complexity of food compounds, the many factors affecting their transition during digestion, and also to the different mechanisms of absorption of water soluble and lipid soluble molecules, unraveling the bioavailability of food constituents is challenging when compared with pharmaceutical drugs[13].

The percentage of nutrients that can be absorbed is related to factors such as function of the digestive system, the shape of the food, the nutrient concentration (ie, the dose given or the non-pharmaceutical dose), the food carrier composition, the intestinal motility and other dietary compositions, as well as other medications[32, 33].

Other factors such as gastrointestinal motility, the lack of developmental function of the intestines of newborns which refer to the individual's health and physiological status, can affect the bioavailability of nutrients[34]. Therefore the individual bioavailability difference depends on several major factors including diet, genetic background, gut microbiota composition and activity[35]. Some bioactive food compounds such as polyphenols, are relatively poorly absorbed, because of low solubility of lipophilic polyphenols in watery foods, their chemical instability at the digestive process and digestion stagesp[36]. Restricted bioavailability prevents the use of bioactive food compounds as functional ingredients [33].

Improving the bioavailability of bioactive food compounds is fundamental to improve their bioefficacy. To obtain this goal many researches on encapsulations technology have been done[35]. Bioactive food compounds undertaken modification technologically and chemically to improve their solubility or the site of absorption, moreover colloidal systems (micelles and vesicles), and nanosystems (nanoparticles) have designed to get efficacy of ingredients [37, 38].

Nanotechnology

Nanotechnology is defined as a material control on a Nano scale, and includes technologies that are used in various scales. Physicochemical properties (such as color, solubility, viscosity, permeability, material tensibility and toxicity) and the biological characteristics of systems and nano-structures differ from the same material at larger scales. Smart packaging materials, efficient delivery systems, improved bioavailable formulations are only part of nanotechnology applications in the food industry[15, 39].

Delivery systems are defined as trapping the bioactive combinations in a carrier to control the release rate of the bioactive compound. Nano-carriers have advantages in comparison to micro-carriers[25, 40]. Nano carriers are roughly single systems disruptions that are stable thermodynamically or exhibit long-term sustainability. In addition of greater surface area, these systems improve the solubility and bioavailability of bioactive compounds, and ultimately could facilitate the control of the release of the bioactive compound in the target tissue, besides avoiding the metabolic modifications that could lead to low absorption[41]. However, it should be noted about an efficacy perspective, that bioavailability characterizations might be influenced by the composition material and the physico-chemical properties of the nanoparticles[2]. Therefore, human studies to identify potential risks of the use of nanoparticles should be taken into consideration.

Nano-carrier systems in the food industry have made remarkable progress same as other industries[42, 43]. These systems are divided into polymer and lipid-based systems. Polymer Based systems, due to the lack of larger scale production

methods, the appropriate biopolymer restriction, need to organic solvents, safety problems and toxicity of polymers is the most limited thus the number of products by these systems is reduced[8].

Nano encapsulation Techniques

Many physicochemical factors affect the bioactive compounds release, which including in: shape and dimensions of carrier, decomposition rate, permeation coefficient of bioactive compound in capsule and medium, polymorphic state of lipid carrier, loading efficiency and PH[44]. Substances such as carbohydrates, proteins and lipids can be used as food carriers. Using of carbohydrates and proteins were restricted due to need for complex chemical and thermal treatments and also the difficulty precise control of these conditions[45]. Therefore lipids are applied because of low toxicity and higher interstitial efficiency[46].

Therefore, it is more necessary to elect the suitable encapsulation technique based on the required size, physicochemical properties, nature of the core material, and wall material[9]. Nano encapsulation techniques can be achieved by both either top-down or bottom-up methods for the development of nanomaterial. A top-down approach involves the choosing of precise tools that cause size reduction and structure shaping for desired application of the nanomaterials being developed[20, 37]. Self-assembly and self-organization of molecules constructed the bottom-up materials, which were affected by many factors including pH, temperature, concentration, and ionic strength [47].

In addition, supercritical fluid technique, inclusion complexation, coacervation, and nanoprecipitation are used in the bottom-up approach [20]. These nanoencapsulation techniques can be used for encapsulation of various hydrophilic and lipophilic bioactive compounds. Emulsification, coacervation, and supercritical fluid technique are used for encapsulation of both hydrophilic and lipophilic compounds [5, 48, 49]. However, inclusion complexation, emulsification–solvent evaporation, and nanoprecipitation techniques are mostly used for lipophilic compounds [50]. In the following, the nonmetric size delivery systems most suitable for food applications, such as Nano emulsions and solid lipid nanoparticles, will be discussed.

Lipid-based Nano-carriers

The most important lipid-based Nano encapsulation methods in the food industry include Nano-emulsions, Nano-liposomes, Solid Lipid Nanoparticle(SLNs), Nano-structure lipid carriers(NLC), and etc, that some of them are discussed in below[51].

Nano emulsions

Nano-emulsions are non-equilibrium systems in which two non-intermixing materials are uniformly convergent. In this system one of the phases is dispersed with very small droplets over the other phase (continuous phase). The nano emulsions have the specificity than to micro emulsions due to the small size of their particles[52, 53]. Nano emulsions have property such as being clearer compared with ordinary emulsions and also stability against droplets accumulation and two phases separation that make them suitable for use in some foods and pharmaceuticals drugs[54]. In general, to produce nano emulsions two methods identified, the high-energy methods (including high pressure homogenization (HPH), microfluidizer and sound waves) and low-energy methods (including self-formation and back-phase methods)[55, 56]. After preparing of the nano emulsions by using the techniques that called the ending techniques, their properties can be changed for the desired application. In recent years, the use of nano emulsions to encapsulate lipophilic constituents and their controlled release (In the exact location and controlled rate and volume) has been widely considered[55, 57]. The release of the compounds can be controlled, by changing the parameters such as the size and composition of the particles and the type of emulsifier. Nano emulsions are better absorbed due to their size, and as a result increases the bioavailability of encapsulated compounds[58]. However this very small particle size can also cause problems such as interfering with the normal functioning of the digestive tract.[59].

The selection of emulsifier type is important to control the interfacial properties (charge, thickness, droplet size and rheology), as well as the response of nanometric oil droplets to environmental stresses (pH, ionic strength, temperature and enzyme activity). Nano emulsions by using the small droplet sizes get highly stabilized to gravitational separation, which means that Brownian motion effects dominate over gravitational forces [60]. Moreover, nano emulsions indicate a lower tendency to droplet aggregation than formal emulsions, because the strength of the net attractive forces acting between droplets usually decreases with decreasing droplet diameters [60]. The nano encapsulation and delivery of bioactive compounds in O/W nano emulsions is an effective approach for dissolution poorly water-soluble compounds in foods. The bioactive molecules, based on the formulation and terms of ingredients, composition, and preparation procedures, might have different localizations within an O/W nano emulsion.

The immobilization of bioactive compounds in the lipid matrix of the nano emulsions, can potentially contribute: (a) to improve the dispersion ability of poorly water soluble compounds in aqueous solutions, prevent or minimizing of the tendency to phases -separation (aqueous and lipid); (b) to protect the bioactive compounds by interaction with food ingredients, keeping their functional properties and inhibiting the spoil of the food itself (i.e., oxidation of fat); (c) to reduce the impact on the organoleptic properties of food; (d) to improve the absorption and bioavailability of the encapsulated bioactive compound, thanks to the subcellular size of the nanocapsules, which enhances passive transport mechanisms (related to the concentration gradient) across the cell membrane[55]. In Table 1, some examples of applications of nano emulsions to the delivery of bioactive compounds are reported, with special emphasis on some of the above aspects.

Table 1. Applications of some nano emulsions to the delivery of bioactive compounds

Bioactives	Formulation/ preparation	Application	Advantages	Ref.
β -carotene	Oil phase: medium chain triglyceride oil emulsifier: Tween 20-80 continuous phase: water Emulsification via high pressure homogenization	Functional food preparation	Improved solubility of carotenoids into aqueous systems	(Yuan et al., 2008)
α -tocopherol	Oil phase: methylene chloride emulsifier: Tween 80 - Span 20 continuous phase: hyaluronic acid and glycerol monostearate solution Emulsification via solvent evaporation	Transdermal delivery vehicles for drugs and cosmetic applications	Enhanced permeability and diffusion into deeper dermis	(Kong et al., 2011)
Curcumin	Oil phase: medium chain triglycerols emulsifier: Tween 20 continuous phase: water Emulsification via high pressure homogenization	Oral administration	Enhancement and targeting of antiinflammation activity	(Wang et al., 2008)

Nano emulsions were also shown to enhance the beneficial effects of encapsulated bioactive compound when orally administered. For example, using a mouse ear inflammation model, anti-inflammation activity of curcumin was shown to be better targeted, when encapsulated in O/W nano emulsions. In particular, the synergistic combination of two key features of the nano emulsion-based delivery system, such as the nanometric droplet size and the presence of a lipid (medium chain triglycerides) in the emulsion formulation, enhanced both the transport through the intestinal walls and cell uptake, allowing the orally-administered curcumin to reach the target sites (the mouse ears) to explicate their full anti-inflammation activity [54]. Additional nano emulsion applications involve sublingual and intranasal delivery of drugs, exploiting the mucoadhesive properties and the ability to enhance the permeability of the mucous layer through an adequate interfacial formulation [41]. The deposition of a multiple layer of emulsifiers and/or polyelectrolytes around nano emulsion oil droplets via layer-by-layer electrostatic deposition technique may positively affect the absorption properties in the gastrointestinal tract [61].

Solid lipid nanoparticles (SLNs)

These types of nano capsules have a solid structure and are produced by the crystallization of nano emulsions and micro-emulsions. SLNs include a solid lipid core with bioactive compounds[62].

These systems are formed by replacing the w/o emulsion oil phase with solid oil or a mixture of solid oils. SLNs N consist of 0.1 to 30 percent solid lipid dispersed in the liquid phase. If necessary, 0.5 to 5% of surfactant will be used.

The average SLN particles ranged from 40 to 1000 nanometers[62].

In general, to produce loaded SLNs, a lipid phase, where the bioactive compounds have been dispersed, is emulsified in aqueous phase at about 10 °C above the melting point of the lipid, via common dispersing techniques, such as colloid milling, ultrasound, solvent evaporation and high-pressure homogenization (HPH). In particular, the HPH technique has emerged as the most reliable and powerful technique for the preparation of SLNs [63]. High-pressure homogenization is more effective than other methods, due to lack of organic solvents usage, less time to produce and empowerment in large-scale compared with other methods.

Homogenization increases the stability of the products, reduces the need for additives and improves the flexibility in loading some medications.

The production of SLNs is carried out in two methods: hot and cold homogenization. In both methods, the compounds are dissolved or mixed with melted fat at a temperature of about 5 to 10 °C above its melting point[64].

The thermal exposure of the encapsulated compounds is minimized, but larger particles and broader size distribution are obtained, in comparison to hot homogenization [63]. The main difficulty associated with the repeatability of the SLNs production is associated to the control of the lipid crystallization, which is significantly dependent on the temperature history of the system, on the presence of impurities in the lipid phase, as well as on droplet size [65]. In comparison to nano emulsions, SLNs exhibit an increased chemical protection against degradation, higher encapsulation efficiency (> 90%) and

a better-controlled release, due to the immobilization of the encapsulated bioactive compound in the solid lipid matrix. As schematically shown in Figure 1.2, the bioactive compounds within solid lipid nanoparticles can be either dispersed in the interstices of the fat crystals (bioactive-enriched core), or on the surface of the lipid nanoparticle protected by the emulsifier layer (bioactive-enriched shell) [23].

Whether a bioactive enriched core or a bioactive enriched shell is formed depends on the solid lipid phase. A lipid phase consisting of fats of different types and with different properties as well as crystallization kinetics, will exhibit an inner core characterized by voids and defects of the crystalline structure, where the bioactive molecules can be preferentially hosted. In contrast, a lipid phase with a more ordered crystalline structure, for example consisting of a single type of fats, will offer less space for the bioactive molecules. In this case, during crystallization upon lipid cooling, the bioactive compounds are phase separated, either enriching the emulsifier shell or being expelled into the aqueous phase. SLNs with a bioactive-enriched core are able to keep the encapsulated bioactive compounds away from any hydrophilic reactive species dispersed in the aqueous phase, as well as to promote a sustained release of the encapsulated active material upon oral administration [66]. On the other side, SLNs with a bioactive-enriched shell are more indicated to provide a delayed release of the bioactive compounds. Typically, two or more lipids with different melting points, e.g., mixtures of purified triglycerides, waxes or fatty acids, are used rather than an individual lipid to increase the loading capacity and retention of encapsulated lipophilic components, which can fit better into the more imperfect crystalline structure formed [67]. Further development of the SLNs brought to the so-called nanostructure lipid carriers, consisting of a disperse phase made of a mix of solid and liquid lipids [66]. The nanostructure lipid carriers, due to the decreased melting point of the lipid phase, can be produced at lower temperatures, reducing the extent of degradation of the thermolabile compounds. Moreover, they are also claimed to have smaller particle sizes than SLNs, as well as to exhibit a sustained release mechanism in the gastrointestinal tract [68].

Nano phytosome

Nanophytosomes are new structures for the transfer of hydrophilic compounds of plant extracts. In that way, these compounds interact with the phospholipid polar portion in a proton-free solvent. The main combination in the structure of nanofitosomes is phospholipid, which produces this structure with its polar part, and increases the efficiency of release of bioactive compounds [69, 70].

Clinical application of nanoencapsulated bioactive components

Bioactive compounds have been shown to have different therapeutic effects, such as antioxidant, anti-inflammatory and anti-cancer properties [25, 71, 72]. However, the use of these compounds has been limited due to low bioavailability and no desired effect [9]. In recent years, the use of nanotechnology has increased in the treatment of diseases, and several studies have examined the nanoencapsulated of bioactive compounds for the treatment of diseases, especially cancers [73, 74]. In a study by Siddiqui et al. have showed epigallocatechin-3-gallate (EGCG) encapsulated in polylactic acid (PLA)-polyethylene glycol (PEG) nanoparticles compared with non-encapsulated EGCG preserved its biological efficacy with over 10-fold dose advantage both in cell culture system and in vivo settings in euthymic nude mice implanted with human prostate cancer cells [75]. Italia and collageous reported epigallocatechin gallate nanoparticles ameliorates cyclosporine induced nephrotoxicity in rats at three times Lower Dose than oral Solution. [76].

Conclusion

One of the important applications of nanotechnology in the food industry is the design and development of functional foods with high solubility, thermal stability, bioavailability, sensory characteristics and physiological performance. Functional compounds or bioactive compounds exist in different foods and have been produced and purified in the past years, but low bioavailability of these compounds has prevented them from benefiting to all their health benefits. Advances in nanotechnology have suggested appropriate solutions to solve of these problems. Nanotechnology has improved in the optimal use of bioactive compounds to enhance bioavailability and delivery of compounds to their target cells.

In recently, different techniques of nano-encapsulation are presented with different degrees of strength and weakness that are gradually identified. Each nano-capsulation technique has some unique factors that affect the amount of final product that these factors need to be investigated and optimized. Most nanocapsules have shown great bioavailability, and only a few numbers of them have inhibitory effects on some of the diseases. On the other hand, the clinical use of nano-capsulated bioactive compounds has greatly improved to treat of some cancers patients in the in vitro and in vivo.

Therefore, it becomes clear that nanoencapsulation of the bioactive food components may have beneficial therapeutic effects, but further studies in vitro and in vivo are demanded to maximize the beneficial and decrease uncomplicated effects of the compounds, as well as an inexpensive and tolerable way for cancer patients.

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