Chapter 4
Micro/Nanoencapsulation of Active Food Compounds: Encapsulation, Characterization and Biological Fate of Encapsulated Systems

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Abstract The micro/nanoencapsulation methods for active food compounds have attracted great interest and opened the door to innovative applications in the food and pharmaceutical sciences. In food science, active compounds have major problems associated with their bioavailability and biocompatibility. These limitations have been overcome through encapsulation approaches, which improve the sensory effect, biocompatibility and bioavailability. Also, the encapsulation of active food compounds enables a protected environment from external conditions. This chapter emphasizes the current know-how and approaches for the production of micro/nanoencapsulation systems for active food compounds and application in new generation foods along with their future progress. We elaborately discussed the importance of micro/nanoencapsulation, the application of complex coacervates, electrospun and electrosprayed micro/nanoparticles, lipid and biopolymeric-based systems with their advantages of encapsulation. Also, this chapter describes the characterization techniques and biological fate of the micro/nano encapsulated systems. In conclusion, the functionality of various micro/nano encapsulated systems is compressively discussed, and future developments are highlighted.

Keywords Microencapsulation · Nanoencapsulation · Active food compounds · Complex coacervates · Lipid based carriers · Biopolymeric micro/nano carriers · Nanoliposomes · Emulsion systems · Electrospun · Polysaccharide-protein complex

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Abbreviations

AG	Acacia gum
AMPS	Allyl methyl disulfide
DLS	Dynamic light scattering
FTIR	Fourier transform infrared spectroscopy
GRAS	Generally recognized as safe
MBAX	Maize bran arabinoxylans
MWAX	Waste water arabinoxylans
O/W	Oil in water emulsion
PEO	Poly (ethylene oxide)
PVA	Poly (vinyl alcohol)
SAXS	Small angle X-ray Scattering
SEM	Scanning electron microscopy
TEM	Transmission electron microscopy
XRD	X-ray Diffraction
β-lg	β-lactoglobulin

4.1 Introduction

Encapsulation of active compounds has attracted great interest in polymer chemistry and various research areas such as food, cosmetic, pharmaceutical and agriculture (Sarıgöl et al. 2017; Sarıgöl et al. 2018; Cota-Arriola et al. 2013). The encapsulation process comprises of entrapment of active compounds within a carrier material (polysaccharide, protein, lipid, biopolymer). The carried matrix is mostly called as shell, capsule, coating and membrane. The encapsulation of active compounds provides a protected environment from external conditions such as heat, light, shear and moisture (Augustin and Hemar 2009). In food science and pharmaceutical applications, the encapsulation method is also used for masking any unpleasant taste or odors of active compounds. Likewise, encapsulation is an efficient approach to control the delivery of the active compounds to the desired area with required concentration and optimal release kinetics (Tampau et al. 2018; Sarigol-Calamak and Hascicek 2018). Encapsulation methods are able to control release mechanisms and kinetics at the desired level and appropriate time with physiological triggers such as heat, light, pH, etc.

In food science, phenolic active compounds (high antioxidant activity) have a major problem with respect to their bioavailability. Also, essential oils have organoleptic problems such as poor water solubility, unpleasant odor and taste. However, such limitations have been overcome through encapsulation approaches, which improve the sensory effect, biocompatibility and bioavailability (Nedovic et al. 2011; Gupta et al. 2016).

The encapsulation carrier materials for active compounds must be biocompatible, food-grade and durable in food systems. The first step for the encapsulation

process is the selection of a suitable carrier matrix. The most commonly used group of materials consists of carbohydrate polymers (cellulose, starch and their derivatives). Plant extracts and exudates include galactomannans, gum, soybean polysaccharides, and pectins. Chitosan, gellan, xanthan, and dextran belong to microbial and animal-derived polysaccharides. This is in addition to lipids and proteins. In the food industry, low-cost carrier materials such as corn starch, gelatin and alginate are mainly preferred (Kavitake et al. 2018; Assadpour and Jafari 2019; Gümüşderelioğlu et al. 2020).

4.1.1 Encapsulation of Active Food Compounds and Its Significance in Food Applications

Encapsulation is an approach that entraps an active compound such as drugs, probiotics, vitamins, antioxidants or living cells within a carrier matrix (carbohydrate, protein, lipids or polymers). Encapsulation enables increase biocompatibility and bioavailability, controlled release of active compounds. Also, it provides odorless and tasteless materials (De Matteis et al. 2019).

Encapsulation methods have attracted great interest in food science and applications for 60 years. An ideal encapsulation should shield the active compound against external conditions, including pH, temperature and ion concentration and enable controlled release of active compounds. In the literature, many techniques have been reported to produce micro/nano encapsulated particles. These methods have their own merits and demerits. For instance, in the emulsion approach, nano-sized particles are produced in the liquid phase that needs an optimum drying process to produce nanocapsules in powder form. Likewise, electrospraying and electrospinning methods are single-step and easy methods for the fabrication of micro and nanocapsules in powder structure. Also, the encapsulation materials intended for food incorporation should contain food-grade ingredients, i.e., materials that are commonly recognized as safe (GRAS) (Bhushani and Anandharamakrishnan 2014). Therefore, proteins, carbohydrates and natural biopolymers are widely used for encapsulation of active compounds due to their biocompatibility and bioavailability. Encapsulated particles are defined as microparticles as the size is between 0.2 and 5000μm, macroparticles when the scale is higher than 5000μm and nanoparticles under 1μm (Akhavan et al. 2018).

4.2 Encapsulation Techniques

Multifunctional micro/nano carries such as emulsion, microcapsules, polymer gels, core-shell capsules and self-assembly structures are mainly used as active compounds delivery systems to increase stability, solubility biocompatibility and

bioavailability of encapsulated active compounds. The selection of the micro/nanoencapsulation method is managed by the physicochemical properties of active compounds (antioxidants, vitamins peptides) and the carrier matrix materials. Encapsulation methods of the active food compounds are classified as physicochemical (coacervation and phase separation and emulsion) and physicomechanical (spray drying, electrospray and electrospinning) methods.

4.2.1 Micro/Nano Encapsulation in Protein-Polysaccharide Complex Coacervates

It has been reported that there are two forms of coacervation: simple and complex coacervations. In simple coacervation, a macromolecule solute phase is transferred to the coacervation phase by changing the condition parameters, including temperature, molecular weight, ionic strength, electrostatic interaction and pH (Fig. 4.1). On contrast, complex coacervation is formed by mixing two oppositely charged ions into two immiscible liquid phases (Kizilay et al. 2011). Polysaccharide-protein complexes are the leading carrier system for the encapsulation of active food compounds. Recently, there has been great attention on potential applications of polysaccharide-protein complexes such as food, cosmetics and pharmaceutical. The electrostatic interactions between oppositely charged polymers control the complex structure during the synthesis.

In complex coacervate systems, soluble protein and polysaccharide form aggregate structure through electrostatic interaction, non-covalent and H-bonding interactivity to minimize the free energy of the complex coacervate during their chemical

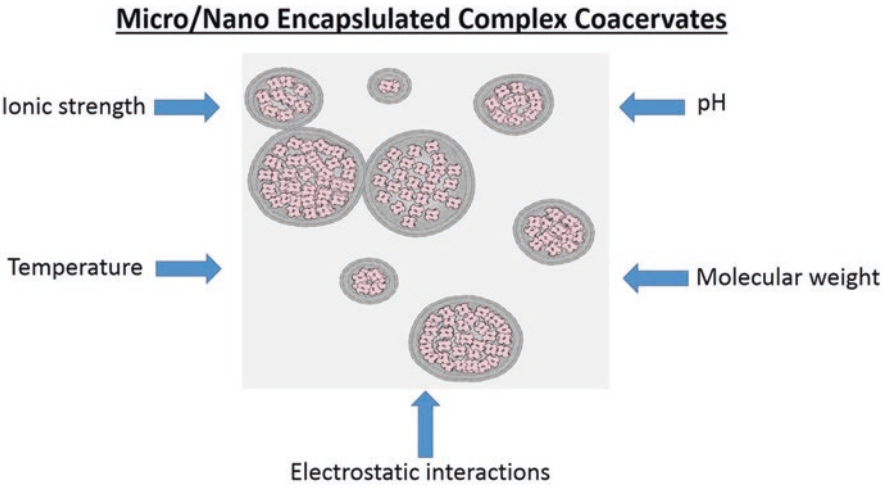

Fig. 4.1 Schematic representation of synthesis parameters which affect the formation of complexes coacervates

and structural properties ensure coacervation (Schmitt and Turgeon 2011). In nature, complex coacervation (polysaccharide-protein complex) can be seen in various living organizations that initiate biological functions. For instance, the sandcastle worm *Phragmatopoma californica* produce sandcastle glue naturally. This process originates from complex coacervation of various oppositely charged proteins and polysaccharides (Zhao et al. 2005; Cooper et al. 2005).

Total polymer concentration, protein and polysaccharide ratio, pH and molecular weight of the proteins and polysaccharides affect the formation of complex coacervation. In addition, the most important thermodynamic parameter is the Gibbs free energy of complex coacervation that increases with an increase in electrostatic enthalpy. Due to its excellent physicochemical properties, biocompatibility and bioavailability, there has been great attention in complex coacervatives for the usage of encapsulation applications. The synthesized complex coacervatives based systems mostly have diameters of nm to mm scale. In the literature, negatively charged polysaccharides and positively charged proteins are widely preferred to form complex coacervates. Schmitt et al. used acacia gum (AG) polysaccharide as a negatively charged molecule, which formed coacervate with β-lactoglobulin (β-lg) (positively charge) (Schmitt et al. 2001).

Polysaccharide-protein based complex coacervates are suitable for most of the active compounds. Their carrier system is able to interact with a great variety of active compounds via their functional groups. In addition, they can be considered as an optimum carrier system if a high-temperature process is required. Polysaccharide structure provides them stability under high temperatures. They are resistant to high temperature compare to lipid-based emulsion systems.

Proteins as carrier matrix have a strong binding capacity to several active compounds via hydrogen bonding and ionic interactions. The functional groups (carboxyl, amine and sulfate groups) of proteins enable physical and chemical surface modifications to designed novel micro/nano encapsulated materials. Likewise, polysaccharides are already widely used as food ingredients and physical, chemical and biochemical properties tailor the processes. Polysaccharides consist of monosaccharides linked by glycosides bonds. The hydrolysis of the polysaccharides results in their constituent oligosaccharides and monosaccharides. Polysaccharides have various functional groups and chemical organizations. A great variety of polysaccharide derivatives can be found in variable molecular weight and linear to branched structure. In nature, they are in amorphous structure and water-insoluble. Cellulose, chitosan, carrageenan, gum arabic, etc. are mainly utilized for complex coacervation of polysaccharides and proteins (Devi et al. 2017). Although coacervation is an expensive method of encapsulation, it can be used for encapsulation of unstable but high-value bioactive substances such as polyphenols and essential oils (Fang and Bhandari 2010).

4.2.2 Spray Drying

Drying is one of the oldest and widely used methods for the protection of foods. By drying methods, the moisture content of the food is reduced and the development of microorganisms and chemical reactions are slowed down (Assadpour and Jafari 2019). Thus, the shelf life of the food extends. Spray drying method was used for the production of milk powder and detergent in 1920s. Spray drying is commonly utilized in food, pharmaceutical, cosmetic, agricultural and chemical industries. This method is fast, cheap, automatize and reproducible method for encapsulating active compounds for food applications. Micro/nano size and encapsulation efficacy depend on several parameters, including solution viscosity, atomizer type, flow rate and inlet/outlet temperature. Suitable materials for the spray drying method should show good drying properties, emulsification and film formation and have low viscosity in concentrated solutions (Chen 2009).

The first step of this process is based on dissolving the active compound and polymer in a suitable solution. After that, the polymer/active compound mixture is put in the atomized heating chamber. This chamber removes the solvent and dried particles are formed. To achieve microparticle production, spray drying uses atomizers and nozzles, which are assisted by pressure. The production of nanosized particles by using conventional spray drying is not possible. To form nanosized particles, a new generation spray drying methods have been developed in these days. The new generation spray drying methods utilize efficient particle collector and a vibrating mesh for ultrafine droplet generation. After nanoparticle production, dried particles are gathered by an electrostatic particle collector. Due to the production process of the spray drying contains heating, this method is not suitable for thermosensitive active compounds. Some carbohydrates such as starch are not suitable because of gelation properties. On the other hand, cyclodextrins and hydroxypropyl cellulose are suitable for spray drying approach at high temperatures (Maurya et al. 2020a).

In food systems, water-soluble dispersions are widely utilized. However, most of the food ingredients are water-insoluble. To cope with this obstacle, the modification of functional groups such as hydroxyl groups of cellulose, chitosan, cyclodextrin lead enhanced water solubility and increased the potential usage of the food carrier matrix (Fathi et al. 2014). Depending on the starting solution and system parameters of spray-drying process result in microparticles, which have a particle size of 1–1000μm. It has been reported that whey protein and casein have attractive coating properties. They have been successfully produced into microparticles integrating anhydrous milk fat, conjugated linoleic acid, avocado oil and probiotic microorganisms (Bae and Lee 2008; Jimenez et al. 2004). The starches such as glucose, lactose, corn syrup and maltodextrin are often incorporated as a secondary carrier matrix to promote drying properties during the spray drying process. They also reduce oxygen permeability of the carrier system and increase the oxidative stability of the encapsulated active compounds (Kagami et al. 2003).

4.2.3 *Electrospray and Electrospinning*

Electrospray and electrospinning methods are widely used to provide biocompatible, biodegradable and food-grade encapsulations of active compounds (Calamak et al. 2015a, b; Çalamak et al. 2014; Ulubayram et al. 2015). These methods utilize electrostatic forces to generate micro/nanofiber and micro/nanoparticles (Fig. 4.2a, b). Both methods work on the same working principle. The polymer concentration and morphology of the final product determine the method. When the solution concentration is high, elongation occurs at the tip of the nozzle (Taylor cone is stable) and nanofibers are formed on the collector. If the polymer concentration is low, the polymer jet destabilized and micro/nanoparticles are produced (Bhushani and Anandharamakrishnan 2014). In the electrospray approach, the polymer solution or liquid, which contains active compounds is atomized by electrical forces. The solvent evaporates during the flight of the micro/nanoparticles through the collector. Electrospray method can fabricate nanosized particles compare to spray drying (Pérez-Masiá et al. 2015).

In recent years, new generation methods have been developed in electrospraying and electrospinning technologies. These methods are coaxial electrospinning or emulsion electrospinning (Fig. 4.2c). Coaxial electrospinning and electrospraying methods enable ultrafine core-shell micro/nanofibers and particles. In this approach, inner capillary nozzle contains an active compound and the shell material comes from the outer capillary nozzle. These new methods enable single-step

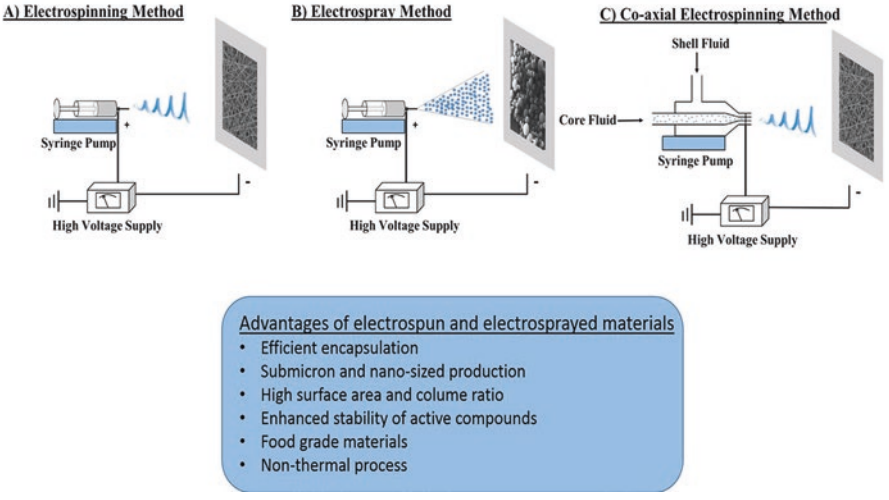

Fig. 4.2 Electrospray, electrospinning and co-axial electrospinning setups; (**a**) Basic electrospinning setup, (**b**) A typical electrospraying setup. Schematic image demonstrates representation of electrospraying process, (**c**) A typical new generation co-axial electrospinning setup. Schematic image shows representation of co-electrospinning process

encapsulation of multiple active compounds with different carrier matrix compared to conventional single nozzle electrospinning.

Electrospinning and electrospray methods provide functional and structural advantages for the encapsulation of active compounds (Mavis et al. 2009). The final particle size can be adjusted by changing system parameters, including polymer concentration, viscosity and dielectric constant. Also, particle size can be controlled by system parameters such as distance between tip (nozzle) and collector, electric field, flow rate and collector material. In addition, the ambient conditions of the system, such as humidity, temperature and chamber air flow affect the particle size.

In the literature, electrospinning and electrospraying methods are well studied as tissue scaffold, drug delivery system and bioelectronics (Maurya et al. 2020a). However, its usage in the field of food science is not well studied. It has been reported that collagen, gelatin, whey protein isolate and whey protein concentrate are widely used as protein sources (Neo et al. 2013; Okutan et al. 2014). Electrospray and electrospinning methods are very suitable for protein encapsulation because these techniques do not require heat that can denature the protein structure. Lopez et al. showed that whey protein concentrate based micro (1724 ± 524 nm) and submicron (83.1 ± 11.5 nm) particles could be produced by electrospray method. In this study, they achieved to encapsulate antioxidant β-carotene. The results showed that the difference in pH of the whey protein solution resulted in significant particle size change. Micro-sized particles were obtained at pH 6.4 (López-Rubio and Lagaron 2012).

Aside from these food active compounds, the food scientists focus on encapsulation methods which enable the stability and viability of probiotic bacteria and bacteriocins for food processing and storage. Many reports have shown that electrospray and electrospinning methods are suitable for encapsulation of living probiotic cells. For instance, Zaeim et al. (2018) investigated the acacia gum encapsulation efficiency by using an electrospray method to protect probiotic cells. To optimize production parameters acacia gum concentration, surfactant addition and physical properties of feed solution were adjusted. It has been shown that increasing gum concentration up to 40 wt% caused to a viscosity increase. At 35 wt.% acacia gum solution containing 1 wt.% Tween-80 concentration ultra-fine, smooth and uniform particles were fabricated by electrospray reinforced drying of the autoclave. In this method thermal sterilization increased the acacia gum solution viscosity and electrospray ability. At the end of the fabrication process, bacterial cell viability results indicated that more than 96% of probiotic cells were alive (Zaeim et al. 2018).

In another study, Paz et al. (2018) reported the production of electrosprayed core-shell arabinoxylan gel particles for insulin and probiotics encapsulation. In this study, electrosprayed core-shell particles consisted of maize bran arabinoxylans (MBAX) with insulin in the core, and maize waste water arabinoxylans (MWAX) with probiotic *(Bifidobacterium)* in the shell. The particles produced with MBAX at 6% (w/v) in the core and MWAX at 10% (w/v) in the shell were obtained more stable and without aggregation with 2.9 mm particle size. The gastrointestinal simulation and insulin release studies indicated that core-shell particles were not digested

in stomach and small intestine and core-shell system was released 76% of carried insulin in the colon (Paz-Samaniego et al. 2018).

Likewise, researchers have been working on the biocompatible composite materials for food applications. Synthetic polymers such as poly (ethylene oxide) (PEO), poly (vinyl alcohol) (PVA) enhance the physical and mechanical properties of the composite carrier materials. Liu et al. (2018) designed a composite film via electrospray method, which consisted of PVA and chitosan. The results indicated that the addition of PVA (75:25:PVA: chitosan) increased elongation at break, oxygen permeability and water barrier properties (Liu et al. 2018).

Electrospinning method does not allow many proteins and carbohydrates to be electrospun alone and needs synthetic polymers and plasticizer to form electrospun jet. In contrast, electrospray does not require any polymer blend or plasticizer. In the literature, it has been reported that the addition of PVA and PEO into electrospinning solution improves electrospinability and fiber formation (Abdel-Mohsen et al. 2019; Son et al. 2020). For instance, the egg albumen protein and low molecular weight collagen do not form fiber development. However, in such a case combining PEO or cellulose acetate with egg albumen provides fiber structure (Wongsasulak et al. 2010; Wongsasulak et al. 2007). The properties of encapsulation material can show a synergetic effect and increase the bioavailability of the active compounds. For instance, electrospun zein fibers enhanced oxidative and light stability of β-carotene was found (Fernandez et al. 2009). In addition, curcumin encapsulated in zein nanofiber (310 nm) enhanced free radical scavenging activity and sustained release properties (Brahatheeswaran et al. 2012).

Nanoparticles provide interesting features compared to microparticles. They have higher bioavailability, enhanced solubility of hydrophobic active compounds and higher surface area (Maurya and Aggarwal 2017). Nanoencapsulated structures can be produced by two different approaches. These are lipid- based vehicles and biopolymer based nanoparticles.

4.2.4 Lipid-Based Micro/Nano Encapsulated Systems for Protection and Delivery of Active Food Compounds

Lipid-based nanoencapsulation approaches are well-studied in the literature and they are widely used for pharmaceutical and food applications. Previous encapsulation approaches were comprised of carbohydrate-protein and biopolymers, which are not good candidates for industrial scale-up due to chemical and thermal processes. Besides, lipid-based nano-carrier matrix can easily be scaled up for industry for food and pharmaceutical applications and enables efficient encapsulation with lower systemic toxicity (Tamjidi et al. 2013).

Most of the active compounds that are used in food applications such as aromas, preservatives, nutraceuticals and vitamins are hydrophobic (Maurya et al. 2020b). Therefore, lipid-based carriers offer higher bioavailability and intestinal absorption

of active compounds. Therefore, lipid-based nano-carriers are known as powerful and flexible delivery agents (Tamjidi et al. 2013). Up to date, several lipid based nano-carriers have been developed. We can classify them into two groups. These are liposomes and emulsions.

4.2.4.1 Liposomes

Liposome term is defined as a spherical amphiphilic lipid carrier, which is consists of an internal aqueous cavity. The production of liposomes includes amphiphilic lipid and aqueous phase interactions. These interactions are led the formation of bilayer structures like cell membrane. The presence of both lipid and aqueous phases provide the encapsulation and delivery of active compounds. The phospholipids comprise of a hydrophobic head and a hydrophilic tail (Fig. 4.3). During the

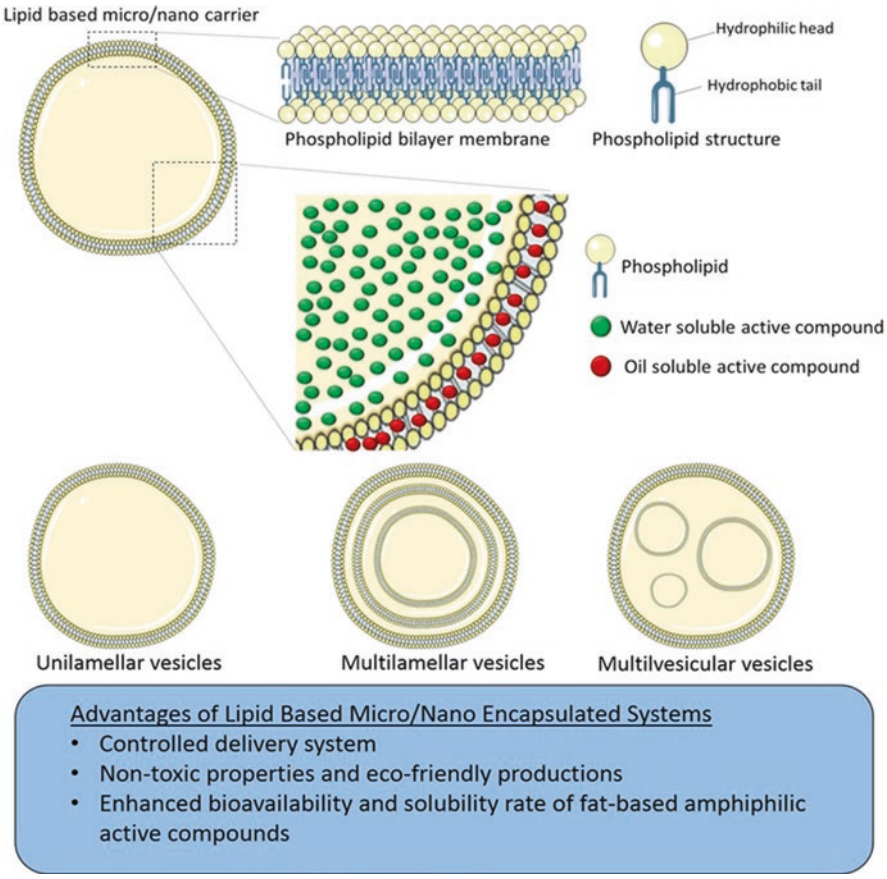

Fig. 4.3 Lipid based micro/nano carrier systems

liposome synthesis, the polar head aligned in the location of the aqueous phase. Liposomes have the ability to mimic cell membrane model due to its bilayer structure and this behavior of liposomes makes them a great candidate for drug formulation and controlled release (Fig. 4.3).

The type of phospholipids, which is mostly used as wall material for liposomes affects the liposome properties. To date, various liposome production methods have been developed in the literature (Lin and Malmstadt 2019; Trucillo et al. 2020). Conventional methods can be listed as thin-film dispersion (Bangham), ethanol/ether injection, probe ultrasonication, bath ultrasonication, reverse phase evaporation, freeze-dried rehydration vesicles, detergent depletion and membrane extrusion methods. Even if these methods offer rapid production and high stability, they require considerable sonication to achieve minimum size limit and longtime processes. To cope with production disadvantages of liposomes such as longtime process and size limits, high-throughput novel methods have been designed by researchers. Novel approaches can be classified as heating method, freeze drying of double emulsions, high-pressure homogenization, microfluidization, supercritical fluid injection and decompression, dual asymmetric centrifugation and dense gas techniques. New generation microfluidic-based methods do not require hazardous solvent and chemicals and may be a proper approach for the preparation of food grade liposomes (Liu et al. 2018; Calamak and Ulubayram 2019; Inci et al. 2018).

Entire production approaches for liposomes include three basic steps; (i) preparation of organic and aqueous phases with active compounds, (ii) drying down lipids from an organic solvent and (iii) purifying the final yield. In food applications, liposomes are typically used as carrier matrix for antioxidants, natural colors, aromas, vitamins and protein delivery (Akhavan et al. 2018). Yang et al. (2013) designed a complex nanoliposome system encapsulating both a hydrophilic drug vitamin C and hydrophobic drug medium-chain fatty acids by double emulsion method with dynamic high pressure microfluidization. The complex nanoliposomes showed high encapsulation efficiency of vitamin C (62.25 ± 3.43%) and relatively high entrapment efficiency of medium-chain fatty acids (44.26 ± 3.34)% with nano-size average diameter (110.4 ± 7.28) nm and excellent storage stability at 4 °C for 60 days (Yang et al. 2013). Shin et al. prepared chitosan-coated curcumin nanoliposomes via ethanol injection method. The entrapment efficiency of curcumin loaded nanoliposomes was 54.70%. The results showed that the encapsulated curcumin provided prolonged absorption in the gastrointestinal tract because of higher mucoadhesion (Shin et al. 2013). In another study, Velez et al. (2019) investigated the effect of lyophilization and rehydration medium on a liposome system for modified with linoleic acid. In this study, liposomes were produced by ethanol injection method employing soy phosphatidylcholine and linoleic acid. They have successfully produced efficient liposomal systems for bioactive compounds delivery in food applications (Vélez et al. 2019). Along with the beneficial attributes, nanoliposomes still have limitations, such as less stability and high cost of food-grade raw materials for nanoliposome.

4.2.4.2 Emulsions

Emulsion systems are mostly water and oil systems, where one of the two immiscible liquids is dispersed in small droplets in the other. The emulsions are classified in different ways depending on the relative dissemination of the oil and water phases in each other (McClements 2010). Emulsions in which oil droplets are dispersed in the water phase; called oil in water emulsions (O/W). The water-in-oil emulsions (W/O) are the ones where water droplets are dispersed in the oil phase. Emulsion systems are classified in three basic categories as macroemulsions (0.5–100 mm) microemulsions (10–100μm) and nanoemulsions (100–1000 nm) according to their particle size. It has been reported that macroemulsions are not thermodynamically stable. Besides, microemulsions are known as thermodynamically stable. However, nanoemulsions are merely kinetically stable (Gu et al. 2005; Doi et al., 2019). The growing interest in the exertion of nanoemulsions has increased significantly over the last decade. The most important advantage of nano-emulsions is the encapsulation of lipophilic functional compounds such as vitamins, flavors, colorants, antioxidants and preservatives (Maurya and Aggarwal 2019b). Lipophilic compounds are generally mixed with the oil phase prior to emulsion production so that when nanoemulsion is produced, these compounds are entrapped in the oil phase. The major components of the food-grade nanoemulsions can be classified as oil, water and surfactant. The optimized mixture of these components determines the properties and stability of the nanoemulsions. Nanoemulsions have high level of lipid moiety along with the scale-up potential with toxicological safety.

Nanoemulsions production techniques are closely related to thermodynamic and physicochemical properties of nanoemulsion systems. These spontaneous systems are produced either by high-energy emulsification and low-energy emulsification. The synthesis approaches for nanoemulsions can be divided as hot homogenization technique, cold homogenization technique, high pressure homogenization, solvent emulsification–evaporation method, solvent emulsification-diffusion technique, microemulsion technique, melting dispersion method, ultrasonication technique, solvent injection and double emulsion technique. Today, many food ingredients exist in the form of nanoemulsions such as sauces, soups, desserts and beverages (Maurya and Aggarwal 2019a; Jafari et al. 2015).

4.2.5 Biopolymeric Based Micro/Nano Encapsulated Systems

Natural biopolymers have attracted great interest in the design of biopolymeric based micro/nano carriers. Among them, hydrogel-based encapsulation methods are widely preferred systems due to their excellent structural and functional properties such as the huge volume of water absorption capacity and the ability for hydrophilic and lipophilic active compound encapsulation (Bourbon et al. 2016; Najafi-Soulari et al. 2016). With their high water absorbance capacity, they can protect the encapsulated active compounds from extreme conditions such as biochemical

degradation and gastrointestinal tract. In a study, thermal gelation of lactoferrin and glycomacropeptide demonstrated good stability at pH 5 and pH 8 with high temperature and salt concentration (Bourbon et al. 2018). In another study Bourbon et al. (2016) designed lactoferrin and glycomacropeptide based curcumin (lipophilic) and caffeine (hydrophilic) loaded nano-sized hydrogel system. The results showed that lactoferrin and glycomacropeptide milk proteins encapsulated more than 90% of curcumin and caffeine with 112–126 nm particle size. The hydrogel-based nanoparticles showed controlled release of both active agent corresponding on pH (Bourbon, Cerqueira, and Vicente 2016). In another study, Wang et al. (2019) investigated encapsulation and controlled release of allyl methyl disulfide (AMDS), which is a lipophilic compound in garlic. It has flavoring, anticancer, antioxidant, and antimicrobial properties. They produced alginate microparticles by injecting a mixture of AMDS-loaded lipid droplets and sodium alginate into a calcium ion solution. Encapsulation of AMDS-loaded lipid droplets in microgels delayed flavor release appreciably (three-fold longer) (Wang, Doi, and McClements 2019). Gomez et al. (2019) developed biopolymeric based carrier materials to increase the storage of the active food compound. For this purpose, they used zein and gelatin as a carrier matrix to encapsulate two model active food compound i.e., epigallocatechin gallate as a model hydrophilic compound and α-linolenic acid as a model hydrophobic molecule. The results showed that encapsulation efficiency was dependent on the chemical structure between the bioactive and shell materials (Gómez-Mascaraque et al. 2019).

4.3 Characterization Techniques of Micro/Nano Encapsulated Systems

Several techniques could be implemented to characterize micro/nanoencapsulated systems. The average size of the microparticles has been generally characterized by Dynamic Light Scattering (DLS) method. DLS technique is based on measuring the intensity and change of light scattered from microparticles in the dilute solution. The change in the intensity of the scattered light depends on the movement and size of the particle and viscosity of medium and the temperature. DLS method is used to obtain hydrodynamic size, diffusion coefficient, distribution index and particle size distribution (Tosi et al. 2020; Dai et al. 2019). Phase-contrast microscopy is used to investigate morphological and structural changes in micro/nanoencapsulated materials. Besides, two and three-dimensional images of micro/nanoencapsulated materials can be visualized by confocal scanning laser microscopy (Mekhloufi et al. 2005; Lamprecht et al. 2000). The structure of micro/nanoencapsulated materials has been investigated by X-ray scattering (SAXS), Fourier transform infrared spectroscopy (FTIR), X-ray Diffraction (XRD) methods and Raman spectroscopy. FTIR and Raman spectroscopy methods include structurally relevant information with the vibrational bands of the materials as well as amorphous and crystalline structure of

the proteins and biopolymers (Weinbreck et al. 2004; Chourpa et al. 2006). These methods also provide extent interactions between the carrier matrix and active compounds. The surface properties and morphology of the micro/nano encapsulated materials such as shape and size have been widely studied by Scanning electron microscopy (SEM), Transmission electron microscopy (TEM) and Cryogenic-TEM (Wei et al. 2017; Baxa 2018; Robson et al. 2018).

4.4 Biological Fate of Micro/Nano Encapsulated Active Compounds

In vitro and *in vivo* models are currently used to determine the biological fate of the micro/nanoencapsulated systems (Mao et al. 2019). Although *in vivo* animal studies are widely used, the collected data are often questioned due to variations in eating habits and physiological conditions of the digestion system between humans and animals (mice, rat, rabbit etc.). Currently, human studies are difficult due to ethical and social considerations. Therefore, *in vitro* systems are increasingly utilized as an alternative to human and *in-vivo* studies. *In-vitro* models can be classified into two sections; static and dynamic models (Bryszewska et al. 2019). The most widely used *in-vitro* models are static models. In these models, conventional laboratory equipment (a shaking and rotary bath) are used to mimic conditions of the stomach and small intestine. Also, these systems require gastro intestinal fluids to simulate digestion behaviors. Although static models are dominantly used for digestion model, none of the static models can mimic the dynamic conditions of the human body (Leyva-López et al. 2019). Compared to static models, dynamic models can mimic the conditions of the human gastrointestinal systems such as pH, enzyme secretion, fluid dynamics and microbial fermentation. The digestion system comprises of three stages: oral processing, gastric digestion and intestinal digestion (Fig. 4.4). The ionic strength, pH and enzyme content of saliva can affect the formation of the active compound encapsulated micro/nanoparticles (Table 4.1).

Enzymes such as pepsin, gastric lipase, protease and pancreatic lipase may affect the degradation of encapsulated materials and adsorption of the encapsulated active compounds. Especially for nanoliposomes and nanoemulsion system, differences in pH and concentration of ionic salts can affect the wall membrane and electrostatic interaction of the lipid based systems (McClements and Li 2010). Besides, digestion and exposure time also play a crucial role for digestion of encapsulated materials. Also, the thickness of the wall material and surface modifications are another two key factors that can significantly affect the degradation behaviors of micro/nanoencapsulation materials (Yu and Lv 2019).

Early studies on the biological fate of mico/nanoencapsulated active compounds were focused on insulin release as a model peptide. It has been reported that free insulin hydrolyzed rapidly after ingestion (Claessens et al. 2008). After encapsulation of insulin with mucin and polyethylene glycol, insulin resisted rapid hydrolysis

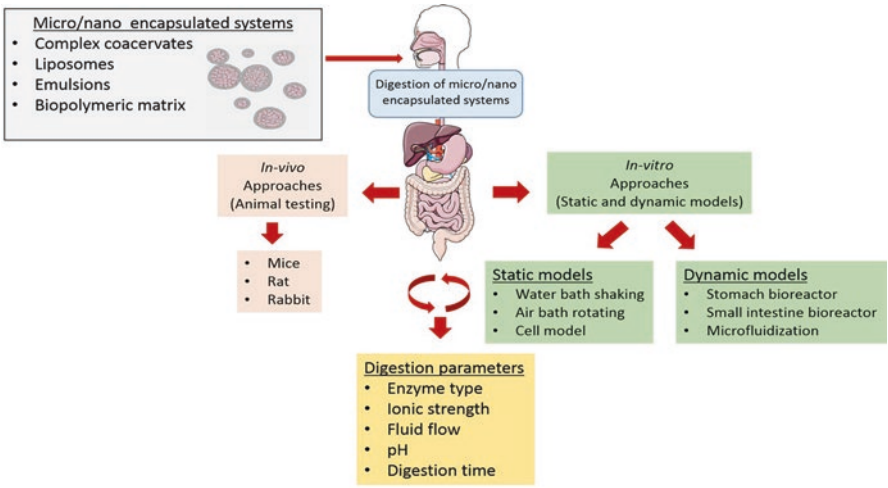

Fig. 4.4 Schematic image of biological fate of mico/nano encapsulated active compounds (Liu et al. 2019)

Table 4.1 Functions and ambient conditions of gastro intestinal system

Digestion system	Functions	Ambient conditions
Oral cavit	Chewing for minimizing the food particles	Enzyme: Amylase, lingual Lipase Saliva flow rate: 0.042–1.83 mL/min (unstimulated), 0.77–4.15 mL/min (stimulated) pH: 5–7
Stomach	Degradation, and chemical Hydrolysis of food particles	Enzymes: Pepsin, gastric Lipase Gastric juice secretion: 1–3 L/day pH: 1–3
Small intestine	Enzymatic catalysis of Macromolecules to Micromolecules and absorption of Nutrients	Enzymes: Pancreatic lipase, Protease, amylase Pancreatic juice secretion: ~ 1.5 L/day pH: 6–7.5
Large intestine and colon	Microbial fermentation and adsorption water	Microbiota:~10^{14} belonging To >1000 different species

and it gained stability in the gastrointestinal system (Iwanaga et al. 1997). Currently, researchers focus on the bioavailability of lipophilic active compounds after *in vitro* digestion. Curcumin is a member of polyphenol compounds and it has water solubility and bioavailability problems (Mutlu et al. 2018). It has been reported that after

surface coating with chitosan and whey protein, the bioavailability of curcumin in small intestines was enhanced compared to free curcumin (Gómez-Mascaraque et al. 2017; Cuomo et al. 2018).

It can be concluded that the interaction of microencapsulated active compounds with other food ingredients and physiological digestion parameters (enzyme, pH, fluid flow etc.) is highly complex. Therefore, in order to clarify the biological fate of the microencapsulated active compounds; (1) there is an urgent need to monitor micro/nanocapsules in food matrices under digestion conditions (2) dynamic digestion models should be preferred and (3) further research is required to clear up the interactions between micro/nanoencapsulated materials and food compounds during the digestion process.

4.5 Future Perspective and Technological Challenges for Micro/Nano Encapsulated Systems

Micro/nanoencapsulation of active compound in food applications exhibit better functionality than conventional protection methods in terms of improved biocompatibility and bioavailability. A great variety of methods have been studied for the encapsulation of active compounds in food applications. However, a few of them i.e., spray drying and lipid- based approaches are widely applied in industrial food applications. Even though every approach has disadvantages with its unique characteristics, which make it challenging, they should be studied elaborately to overcome their limitations and enhance their level from laboratory bench scale to food industry scale. Nanoscale encapsulated materials are a promising approach that increases biocompatibility and bioavailability of active compounds and prolong retention time. To the best of our knowledge, the most suitable nano-sized carrier materials for food engineering are carbohydrate-polymer complexes and lipid-based emulsion systems. Besides, spray drying is the most preferred method. It is possible to make large-scale production with spray drying, which is widely available in the food industry. The successful encapsulation of active compounds mainly depends on the selection of carrier materials and encapsulation techniques. Polysaccharides and proteins offer an advantageous formulation for the micro-size encapsulation of active compounds by using spray drying and emulsion techniques. On contrary, electrospinning and electrospraying methods provide micro/nano sized high encapsulation efficiency, controlled release profile and increased thermal, oxidative and light stability. The digestion of micro/nanoencapsualtion materials and active compounds depends on other food ingredients, physicochemical properties of encapsulation materials, food intake time and gastrointestinal conditions such as age, sex and health status. To date, most micro/nanoencapsulation systems which have been developed, comprising of one active compound. On contrary, new generation food systems are much more complex and consisting of active compound mixtures. Therefore, further research on micro/nano encapsulation systems should focus on complex micro/nanocarriers for food science.

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