Chapter 20
Encapsulation of Bioactive Compound and Its Therapeutic Potential

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Abstract Micro- or nanoencapsulation has become one of the most attractive approaches to enhance the stability and bioavailability of bioactive compounds isolated from natural products. In addition, such encapsulation also provides an opportunity to modulate the release of bioactive compounds by using functional polymers that can be fine-tuned according to the need of the body. Over the last 10 years, increasing research works have been dedicated toward the encapsulation of bioactive compounds for various purposes. Numerous techniques, embracing micro- and nanoplatforms including spray drying, freeze drying, micro- and multiple emulsification, electrospinning, and coacervation, have been utilized to achieve the encapsulations. Such encapsulations have been found to improve the physicochemical properties of the bioactive compound, provide stability and enhanced bioavailability, controlled release of the compound, enhancing bioactivity, and masking of flavor or taste, along with several other benefits. Wide ranges of materials including lipids, synthetic, and natural polymers have been utilized, and the type and amount of the wall formers have been found to influence the performance and functionality of these preparations.

Keywords Encapsulation · Bioavailability · Bioactive compounds · Hydrogels · Electrodynamic processes

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20.1 Introduction

Phytochemicals in plants that produce therapeutic activities are collectively known as bioactive compounds. These bioactive compounds are predominantly plant secondary metabolites and nutrients such as vitamins and minerals that may induce pharmacological activity at high doses are usually excluded from the definition of bioactive compounds (Bernhoft 2010). Abundant bioactive phytochemicals are found in vegetables, fruits, seeds, nuts, legumes, leaves, and other parts of plants (Al Juhaimi et al. 2018; Pachuau et al. 2019; Sagar et al. 2018; Septembre-Malaterre et al. 2018; Xiao and Bai 2019). Phenolic compounds such as flavonoids, courmarins, phenolic acids, xanthones, and ellagitannins along with alkaloids, phytosterols, carotenoids, anthocyanins, and tocopherols are some of the commonly found bioactive compounds from plant sources that are responsible for their bioactivities (Fig. 20.1) (Altemini et al. 2017; Da Silva et al. 2016; Xiao and Bai 2019). In addition to their bioactivities, phytochemicals such as phenolics in vegetables and fruits may also contribute to their stability against oxidation, taste, color, flavor, and odor (Naczk and Shahidi 2006).

Studies have reported myriads of pharmacological activities including antimicrobial, anti-hyperglycemic, anti-inflammatory, antioxidant, anti-proliferative, and anti-diabetic effects of bioactive phytochemicals isolated and characterized from various plant species (Martins et al. 2016; Ramesh Kumar et al. 2018; Rodriguez-Garcia et al. 2017). Diverse preparations made from these wide varieties of plant species have been used in the treatment of different diseases since ancient times as documented in Eber's Papyrus, Traditional Chinese Medicines (TCM), and Ayurvedic formulations (Atanasov et al. 2015; Khan et al. 2019; Yang and Yue 2012). These traditional practices still remain valuable sources of information for modern drug discovery and development programs. In fact, data from Food and

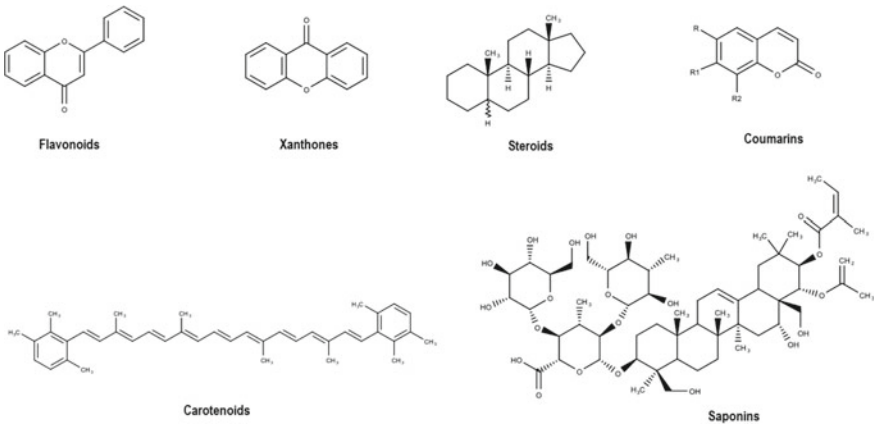

Fig. 20.1 Structures of some phytochemicals

Drug Administration (FDA) revealed that about 40% of the approved molecules are either natural compounds or inspired by them and, from these, 74% are indicated for anticancer therapy (Seca and Pinto 2018). Still, it has been reported that about 95% of the world's biodiversity are yet to be systemically investigated for their pharmacological activity and only 15% have been evaluated phytochemically (Atanasov et al. 2015; David et al. 2015). The current global scenario and the urgent need for effective therapy to treat chronic as well as infectious diseases including cancer and HIV implied that natural products will continue to play a pivotal role in drug discovery and development processes (Cragg and Newman 2013).

Although natural products are considered to be safe and their bioactive phytochemicals exhibit excellent pharmacological activities in vitro, they often failed to translate this into clinical or therapeutic effects in vivo. The major problems associated with bioactive phytochemicals include their low oral absorption and rapid systemic clearance which ultimately lowers their bioavailability and therapeutic efficacy in vivo (Kumar et al. 2010; Rein et al. 2012). For instance, oral administration of curcumin at 500 mg/kg in Sprague-Dawley rats produced maximum plasma concentration (C_{max}) of 0.06 ± 0.01 μg/ml after 41.7 ± 5.4 min (Yang et al. 2007), while in healthy human volunteers, curcumin was detected in the serum only when it was administered orally at a dose higher than 8 g (Lao et al. 2006). Similarly, other potent bioactive compounds such as quercetin (Almeida et al. 2018; Kasikci and Bagdatlioglu 2016), paclitaxel (Malingre et al. 2001; Tiwari and Amiji 2006), and ellagic acid (Bala et al. 2006; Lei et al. 2003) also produced extremely low oral bioavailability eventually resulting in suboptimal oral therapy in vivo. Predominant factors that led to the poor oral absorption of these natural bioactive compounds are their eminently low aqueous solubility, poor dispersibility, and bioaccessibility which are the prerequisites for absorption through the gastrointestinal (GI) tract. For example, the maximum solubility of curcumin in aqueous buffer pH 5.0 is only 11 ng/ml (Ma et al. 2019) and the aqueous solubility of ellagic acid is about 9.7 μg/ml (Alfei et al. 2019). In addition, instability of various bioactive compounds on exposure to environmental factors such as pH, enzymes, light, heat, oxygen, and moisture may also contribute to their degradation in vitro and in vivo (Bohn et al. 2015; Islam Shishir et al. 2018). Moreover, biological factors including permeability of the intestinal epithelium, the presence of efflux transporters such as P-glycoprotein and the induction or inhibition of metabolizing enzymes may also serve as barriers to oral bioavailability of several bioactive compounds (Chu et al. 2008; Ma et al. 2019; Xie et al. 2011). Overcoming these challenges has become one of the most important focuses of the current research on improving the oral bioavailability of bioactive compounds. Techniques such as micronization (Aguiar et al. 2018) or nanonization (Aditya et al. 2019; Borhan et al. 2014) to reduce the particle size, co-administration of phytochemicals with bio-enhancers such as piperine (Gorgani et al. 2017), micro- and nanoencapsulation with different types of coating materials (Dias et al. 2017; Ezhilarasi et al. 2013) are some of the approaches designed to achieve the oral bioavailability enhancement of bioactive compounds.

The process of applying relatively thin coatings around a substance which may be solids, liquids, or even gases is called encapsulation. Based on the size of the coated particles, the process may be microencapsulation or nanoencapsulation. Encapsulation separates the encapsulated materials also known as the core materials from the environment with the help of a coating material, usually a polymer. Thus, encapsulation provides protection of the core material and it may also add certain functionalities such as color for identification, masking of taste, or sustaining the release of the core materials. As a result, micro- or nanoencapsulation has become an indispensable technology in various industries including pharmaceuticals, cosmetics, nutraceuticals, and agriculture.

Encapsulation is one of the techniques that can be applied to enhance oral bioavailability, solubility, dispersibility, and stability of bioactive compounds (Beevers and Huang 2011; Ezhilarasi et al. 2013; Gomez-Estaca et al. 2015; Li et al. 2015; Shaikh et al. 2009). Numerous methods have been applied in the encapsulation of various natural bioactive compounds utilizing wide range of coating materials such as lipids, natural, and synthetic polymers (Anirudhan and Binusree 2016; Islam Shishir et al. 2018; Oehlke et al. 2017; Pinho et al. 2013; Shao et al. 2011; Sharma et al. 2007; Young et al. 2005). The selection of the coating materials is critical as the size, shape, and stability of the final encapsulated product as well as the release characteristics of the core material is largely determined by the type and amount of the coating materials used (Dias et al. 2017).

20.2 Rationale for Encapsulation of Bioactive Compounds

Encapsulation of natural bioactive compounds into various nano- or micro-platforms has the potential to resolve several drawbacks that are inherent to these phytochemicals. This may range from improving their physicochemical properties such as solubility and stability, to their pharmacokinetics such as absorption and the overall bioavailability. Some of the advantages offered by encapsulation of bioactive compounds can be summarized as follows:

(a) *Enhanced bioavailability and therapeutic activity*: Improvement in bioavailability of poorly absorbable phytochemicals such as polyphenols has been reported after their encapsulation into various systems such as solid lipid nanoparticles (SLN), micelles, liposomes, and others (Aqil et al. 2013; Murugan et al. 2009; Puligundla et al. 2017; Xie et al. 2011; Yang et al. 2008). This enhancement in bioavailability can be manyfold, as at least ninefold increase in oral bioavailability had been reported for poly(lactic-co-glycolic acid) (PLGA) nanoencapsulation of curcumin (Shaikh et al. 2009), while 942.53% enhancement in relative bioavailability was also reported for curcumin encapsulated in SLNs (Ji et al. 2014).

(b) *Stability*: Most of the bioactive compounds from plants are susceptible to light, heat, and pH changes developing unpleasant flavor or colors (Alborzi et al. 2012; Fang and Bhandari 2010; Prakash et al. 2018; Rezaei et al. 2019; Soukoulis

and Bohn 2018). Encapsulation can prevent in vitro or in vivo degradation of bioactive compounds against these factors.

(c) *Taste masking*: Food or therapeutic applications of several phytochemicals have been limited by their unpleasant flavor, astringency, and bitter taste (De Souza et al. 2020). Encapsulation can eliminate this problem as the bioactive compound is not in contact with the taste buds located in the oral cavity. For instance, microencapsulation of quercetin with carnauba wax, shellac, or zein was able to reduce or mask the bitter taste of the compound (Khor et al. 2017), while the flavor of turmeric extract was effectively masked by brown rice flour and β-cyclodextrin-based microcapsules (Laokuldilok et al. 2016).

(d) *Improvement of physicochemical properties*: Micro- or nanoencapsulation offers the opportunity to improve the overall physicochemical properties such as morphology and wettability, presenting bioactive compounds into spherical, uniform size, and free-flowing powders which also facilitate their processing during manufacturing (Bertoni et al. 2019; Dima et al. 2016; Lu et al. 2011). Such improvement in powder flow property reduces the possibility of variation in the quality of the end products (Guajardo-Flores et al. 2015). Dissolution rate of poorly aqueous-soluble phytochemicals such as naringin and quercetin has also been reported to be enhanced by 20–55% (Pai et al. 2015) and 100 times (Barras et al. 2009), respectively, probably due to the dispersion of the bioactive compound in amorphous form within the matrix.

(e) *Controlled or targeted release of bioactive compounds*: Encapsulation enables controlled and targeted release of the encapsulated bioactive molecules, protecting against degradation and first-pass metabolism while enhancing their bioactivity following oral administration (Goiun 2004; Moreno et al. 2018; Sun et al. 2015; Yao et al. 2015) (Table 20.1).

20.3 Encapsulation of Bioactive Compounds

20.3.1 Microencapsulation

Microencapsulation is one of the most common methods employed to provide wide range of functionalities including protection of bioactive compounds against environmental factors and to enhance their bioavailability (Table 20.2). It is also possible to encapsulate bioactive oils such as essential oils and is a means of converting these oils into free-flowing powders which facilitate its handling, stability, and bioactivities. Due to their small and uniform particle size, microcapsules are distributed homogenously along the GI tract which promote absorption of their encapsulated compounds and enhance oral bioavailability (Lengyel et al. 2019). Various methods such as spray drying (Boonchu and Utama-ang 2015), spray congealing (Tomsik et al. 2019), coacervation phase separation (Silva et al. 2011; Jain et al. 2015), solvent evaporation (Paulo and Santos 2018; Sawale et al. 2017),

Table 20.1 List of some bioactive compounds with nanoencapsulation technology for improved characteristics

Bioactive compound	Encapsulation type/ techniques	Improvement after encapsulation	References
Eugenol	Oil-in-water emulsion and ionic gelation	Thermal stability	Woranuch and Yoksan (2013)
Curcumin	Nano-precipitation	Solubility and antioxidant activity	Dutta et al. (2018)
	Nanoemulsion	Solubility and stability	Ahmed et al. (2012)
	Liposomes	Increased bioavailability compared to suspension	Takahashi et al. (2009)
Caffeic acid	Inclusion complex by β-cyclodextrin	Enhanced bioactivity	Pinho et al. (2015)
	Liposomes	Enhanced antioxidant properties	Katuwavila et al. (2016)
Chlorogenic acid	Nanoparticles by ionic gelation techniques	Sustained release property, retained antioxidant activity, and enhanced bioavailability	Nallamuthu et al. (2015)
	Liposomes	Enhanced oral bioavailability, increased antioxidant properties	Feng et al. (2016)
Coumaric acid	Nano-sized multi-phase emulsion	Increased stability and bioaccessibility, sustained release	Huang et al. (2019)
Resveratrol	Nanoemulsion by high-pressure homogenization	Solubility, stability, and bioavailability	Sessa et al. (2014)
Quercetin	Solid lipid nanoparticle	Increased bioavailability	Li et al. (2009)
	Microemulsion	Increased bioavailability	Sun et al. (2010)
	Nanoliposomes by film-sonication	Enhanced bioactivity, enhanced release	Rodriguez et al. (2019)
Capsaicin	Nanoemulsion	Increased bioavailability	Choi et al. (2013)
Retinoic acid	Solvent evaporation	Controlled release	Ezpeleta et al. (1996)
Ellagic acid	Emulsion–diffusion–evaporation	Sustained release, enhanced bioavailability	Mady and Shaker (2017)
Sesamol	Phosphatidyl choline micelles	Enhanced bioavailability and bioactivity	Yashaswini et al. (2017)
d-limonene	High-pressure homogenization	Enhanced antimicrobial activity	Donsi et al. (2011)
Carvacrol	Liposome/lipid film hydration technique	Sustained released, increased activity	Engel et al. (2017)

(continued)

Table 20.1 (continued)

Bioactive compound	Encapsulation type/ techniques	Improvement after encapsulation	References
Thymol	Liposome/lipid film hydration technique	Sustained released, increased activity	Engel et al. (2017)
Naringenin	Liposome/thin film hydration	Enhanced solubility and bioavailability	Wang et al. (2017)

Table 20.2 Reasons for microencapsulation of bioactive compounds

Reasons
To minimize bitterness and astringency of bioactive compounds
Encapsulation of bioactive fixed and essential oils
Controlling of organoleptic properties such as color, flavor, and odor
Protection against degradation due to oxidation, pH, enzymatic reactions, etc.
Controlled release and improved therapeutic activity of bioactive compounds
Ease of administration
Improvement in physicochemical properties
Enhance dissolution rate

and ionic gelation (Borgogna et al. 2010) have been utilized for encapsulating bioactive compounds. Wide range of wall-forming materials from natural and synthetic sources have been used in microencapsulation of bioactive compounds and the nature and quantity of these wall formers determined, to a large extent, the quality and functionality of the resultant microcapsules.

In an ideal delivery system, the bioactive compounds should not be allowed to affect the color or flavor or interact with the sensory organs and also the particles are presented small enough not to interfere with the texture (Champagne and Fustier 2007). Microencapsulation is a technology to achieve this objective in effective delivery of bioactive compounds. An extract of *Gentiana lutea* root containing bitter secoiridoids was coated with ethylcellulose–stearate system into microcapsules and was found to mask the bitterness in the mouth and the release of the bioactive compound in the GI effectively reduces the daily energy intake in human subjects (Mennella et al. 2016). Not only with the bitter taste alone, natural compounds often come with strong odor or flavor, leaving behind a sensation of astringency. Apart from enhancing its stability, the strong flavor and astringency of cinnamon extract, a rich source of proanthocyanidins, were successfully concealed by microcapsulation with gelatin/gum arabic and gelatin/κ-carrageenan systems (De Souza et al. 2020).

Spray drying is one of the most common methods employed for microencapsulation of bioactive compounds. Spray drying was employed to effectively encapsulate both the seed oils and peel extract of pomegranate to provide protection of the phenolics and fatty acid contents which are otherwise highly sensitive to

environmental factors during their storage (Bustamante et al. 2017). Procyanidins extracted from grape seed oil was also encapsulated by spray-drying method using gum arabic and maltodextrin as coating materials and in this manner, the stability and shelf-life of the product were enhanced (Zhang et al. 2007). When freeze drying was compared against spray drying for microencapsulation of bioactive compounds extracted from *Hibiscus Calyces* using various encapsulating materials, encapsulation of anthocyanins was higher with freeze drying using gum arabic and yields higher antioxidant activity, while in terms of physical properties, better results were obtained with spray-drying method (Piovesana and Norena 2018).

Another improvement that microcapsules offered is the prospect of enhancing the solubility, and hence the oral bioavailability of bioactive compounds. Spray-congealing microencapsulation of wild garlic (*Allium ursinum* L.) extract was found to enhance the aqueous solubility more than 18 times of the pure extract, and in addition, there was only a minor decrease in the content of the bioactive compounds, allicin, and S-methyl methanethiosulfonate over 3-month period of storage (Tomsik et al. 2019). Microencapsulation also provides the opportunity for sustained or controlled release of bioactive compounds for prolonged therapeutic activity (Jain et al. 2015; Saifullah et al. 2019).

20.3.2 Nano-based Encapsulation Platforms for Bioactive Compounds

Various nanotechnology-based platforms have been developed to overcome the low oral bioavailability, systemic toxicity, or stability problems facing bioactive compounds. Enhancing oral bioavailability has been one of the major objectives of these nanomedicinal preparations. The main focus of such enhancement schemes encompasses the three oral bioavailability requirement steps like increasing the aqueous solubility of bioactive compounds, enhancing the lipid partitioning or permeability and reduction of first-pass metabolism (Pachuau 2019). Studies have shown that encapsulation of bioactive phytochemicals in various nanoparticulate systems was successful in achieving these objectives by controlling their release, facilitating their systemic absorption, bypassing pre-systemic metabolism, and enhancing the cellular uptake while also providing their stability (Ahmed et al. 2012; Aqil et al. 2013; Mukherjee et al. 2015).

20.3.2.1 Polymeric Nanocapsules

Nanocapsules differ from microcapsules only in their size; however, reduction of particle size to nanometer range leads to remarkable advancement in their physicochemical properties. Nanoencapsulation enhances dissolution of the drug, membrane permeability stabilization of labile drugs, and controlled release of the

encapsulated drug (Pandey et al. 2005). As a result, polymeric nanocapsules facilitate both oral and parenteral administration of bioactive compounds. The type and amount of the wall formers in nanocapsules have been shown to influence the size, surface properties, stability, drug-loading capacity, aqueous solubility, and the release profile of the encapsulated compounds (Dos Santosa et al. 2016). Therefore, selection of appropriate wall-forming material is crucial to impart the desired functionality to the nanocapsules. Biocompatible and biodegradable poly(lactic acid) (PLA), poly(glycolic acid) (PGA), and their copolymer poly (lactide-coglycolide) (PLGA) are among the most commonly used polymers for nanoencapsulation (Liu and Feng 2015). Encapsulation of ellagic acid in PLGA nanoparticles was found to increase the intestinal permeability from 66% in aqueous suspension of ellagic acid from to 87% in nanocapsules while also exhibiting its antioxidant effects (Bala et al. 2006). PLGA-based silymarin nanocapsule was also shown to sustain the release, improve bioavailability, and exhibit preferential toxicity toward prostate cancer cells, thus enhancing its overall therapeutic efficacy (Snima et al. 2014). Nanoencapsulation of curcumin with PLGA also delayed the progression of diabetic cataract in animal model (Grama et al. 2013) (Table 20.3).

Poorly aqueous-soluble anticancer phytochemical paclitaxel, isolated from *Taxus brevifolia*, which also suffers from P-glycoprotein-mediated efflux and metabolism by cytochrome P450 metabolic enzymes (Singla et al. 2002), had been alleviated through nanoencapsulation. The improvement in permeability of nanoencapsulated paclitaxel across Caco-2 monolayers was found to be 6.7–7.4 times of the lone paclitaxel and the plasma concentration time curve (AUC) and C_{max} following oral administration also increased up to 5.7 times and 7.3 times, respectively (Iqbal et al. 2011).

Coating with mucoadhesive polymers is another means to improve oral bioavailability of bioactive compounds due to their ability to bring prolonged and intimate contact with GI tract surfaces resulting in better absorption. Chitosan has often been used to coat the polymeric nanocapsules due to its ability to adhere to the negatively charged mucosal surface, thus improving absorption and hence therapeutic activity (Chuah et al. 2014; Ensign et al. 2012; Mazzarino et al. 2012).

Capsaicin is a natural bioactive compound isolated from peppers with pungent odor and quick degradation and nanoencapsulation with natural wall formers gelatin and acacia was able to mask the pungency and instability of capsaicin (Jincheng et al. 2010; Wang et al. 2008). pH-dependent release and thermal stabilization of bioactive compounds have also been achieved using natural-based encapsulating materials (Akbari and Wu 2016; Pinheiro et al. 2015).

20.3.2.2 Solid Lipid Nanoparticles (SLN) and Nanostructured Lipid Carriers (NLC)

Lipid-based nanocarriers like SLNs have become effective alternative delivery systems to conventional colloidal carriers like emulsions, liposomes, and polymeric

Table 20.3 Various methods for microencapsulation of bioactive compounds

Methods	Bioactive compounds	Coating materials	Particle size (μm)	Percent encapsulation (%)	Purpose
Spray drying (Mennella et al. 2016)	*Gentiana lutea* root extract (secoiridoids)	Ethylcellulose and stearate	–	–	Bitter-taste masking
Spray-drying (Boonchu and Utama-ang 2015)	Grape (*Vitis vinifera* L.) pomace extract	Maltodextrin and Carboxymethyl-cellulose	–	–	Masking of bitterness and astringency
Spray drying (Bustamante et al. 2017)	Pomegranate (*Punica granatum* var. Wonderful) peel extract and seed oil	Capsul C (modified starch)	4.34–4.67	35.1–92.7	Stabilization
Spray drying (Zhang et al. 2007)	Grape seed extract (Procyanidins)	Gum arabic and maltodextrin	5–30	88.84	Stabilization
Spray drying and freeze drying (Piovesana and Norena 2018)	Bioactive compounds from *Hibiscus calyces* extract	Partially hydrolyzed guar gum, poly-dextrose, gum arabic	5.43–143.08	59.84–74.28	Improvement of physical properties
Spray drying (Romo-Hualde et al. 2012)	Bioactive compounds from red pepper (*Capsicum annum* L.)	Gum arabic	5.46	63.60–77.10	Stabilization
Spraydrying (Saenz et al. 2009)	Bioactive compounds from cactus pear (*Opuntia ficus-indica*)	Maltodextrin and inulin	–	39.41–99.49	Stabilization
Double emulsion solvent evaporation (Paulo and Santos 2018)	Caffeic acid	Ethylcellulose	1.4–298	65.9–92.3	Controlled release cosmetic formulations
Spray congealing (Tomsik et al. 2019)	Wild garlic (*Allium ursinum* L.) extract	Gelucire 50/13 (Stearoyl polyoxyl-32 glycerides)	100–200	99	Stability and oral bioavailability
Complex coacervation (Jain et al. 2015)	β-Carotene	Whey protein isolates and gum acacia	1–500	70	Controlled release

micelles (Lin et al. 2017). In SLNs, the bioactive compounds are part of the solid lipid core matrix (Fig. 20.2) which is stabilized by a surfactant or a mixture of surfactants (Weiss et al. 2008). They provide a safe means of effective delivery system for poorly aqueous-soluble bioactive phytochemicals, enhancing their stability while also promoting their permeability and bioavailability. They originate from an O/W-type emulsion where the liquid oil (lipid) is replaced by solid oil that remains solid at body temperature (Akhavan et al. 2018). SLNs are biocompatible, considerably stable with good encapsulation efficiency, and can prolong the release of the encapsulated compounds (Akhavan et al. 2018; Weiss et al. 2008). The surface of SLN can also be functionalized with agents to facilitate their uptake and targeting the release of the drug to the desired site of action (Ganesan et al. 2018). In addition, SLN can also carry both lipophilic and hydrophilic drugs and can be sterilized and produced in large scale (Liu and Feng 2015). Nanostructured lipid carriers (NLC) are new generations of SLNs developed in the 1990s which incorporate a mixture of solid and liquid lipids to overcome the limitation of SLNs in effective drug delivery (Akhavan et al. 2018). NLCs improve the bioactive retention capacity of these nanostructures and facilitate controlled release of the bioactive compounds.

Stabilization to oxidation offered by SLNs seemed to depend on the physicochemical properties of the encapsulated bioactives. Within the SLN, hydrophobic and high melting bioactive compounds like β-carotene are reported to be located within the inner matrix and kept at the α-subcell of the crystal structure thereby protecting it from oxidation, while less hydrophobic compounds like vitamin A arranged on the surfaces of the SLN leading to rapid oxidation (Salminen et al. 2016). However, between the SLNs and NLCs, NLCs were reported to provide better stability to β-carotene than the SLNs (Qian et al. 2013). The tendency of droplets aggregation and to coalescence still exists in SLNs which have the capacity to expel the encapsulated β-carotene to the particle exterior on storage, making it sensitive to degradation than when it is encapsulated in NLCs.

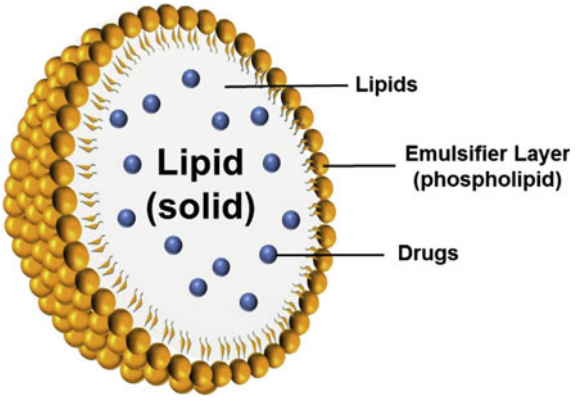

Fig. 20.2 Structures of solid lipid nanoparticles (SLNs) (Reproduced with permission from *Lin* et al. 2017, Copyright © Food and Drug Administration, Taiwan. Published by Elsevier Taiwan LLC)

Flavonoids like quercetin and resveratrol suffer from low aqueous solubility, rapid metabolism, and photosensitivity which limited their oral bioavailability when taken orally (Li et al. 2009; Pandita et al. 2014). Formulation of quercetin into SLN remarkably enhances its gastrointestinal absorption and pharmacokinetic study in animal model demonstrated that the relative bioavailability of the SLN formulation against the quercetin suspension 571.4% indicating phenomenal increase in its oral bioavailability (Li et al. 2009). Stearic acid-based SLN of resveratrol was also reported to increase the oral bioavailability of the bioactive compound by eightfolds when compared to its suspension. Similarly, oral bioavailability of curcumin was also increased in a dose-dependent manner when formulated into soy lecithin-based SLN in animals. Improvement in oral bioavailability of curcumin-loaded SLN against solubilized curcumin rat plasma was reported to be 155 times at the dose of 1 mg/kg, 59 times at 12.5 mg/kg, 32 times at 25 mg/kg, and 39 times at the dose of 50 mg/kg (Kakkar et al. 2011). Bioavailability enhancement through SLN formulation has also been reported for other bioactive phytochemicals like an alkaloid vinpocetine which exhibit poor aqueous solubility and extensive first-pass metabolism (Luo et al. 2006; Medina 2010). Oral bioavailability from SLN vinpocetine formulation was found to be 4.16–4.17 times that of the suspension (Luo et al. 2006).

Recently, SLN-based sclareol was prepared following hot homogenization technique and evaluated its anti-proliferative activity in vitro against A549 human lung epithelial cancer cells which showed similar cytotoxicity to the plain sclareol but long-term stability and sustained release of sclareol were obtained with the SLN formulation (Hamishehkar et al. 2018).

NLC-based formulations also exhibit promising results in enhancing bioavailability of bioactive compounds. Silymarin was encapsulated in NLC-based formulation using glycerol distearates, oleic acids, lecithin, and Tween-80, which increases the oral bioavailability of silymarin against solid dispersion pellets and commercially available silymarin preparation, Legalon®, was 2.54- and 3.10-folds, respectively (Shangguan et al. 2014). However, when NLC was compared against microemulsion in its capacity to enhance oral bioavailability of luteolin in animal model, microemulsion fared better than the NLCs (Liu et al. 2014). The relative bioavailability of NLC-based and microemulsion-based luteolin formulations to the luteolin suspension were found to be 515.06% and 885.46%, respectively.

20.3.2.3 Liposomes and Phytosomes

Both liposomes and phytosomes are also lipid-based formulations suitable to facilitate the delivery of poorly aqueous-soluble phytochemicals. Liposomes are spherical vesicles (15–100 nm) consisting of phospholipid with a liquid core and variable layers, where the hydrophobic tails of the phospholipids face each other, while the hydrophilic heads are projected toward the inner aqueous core or the outside boundary of the liposome (Fig. 20.3) (Bonechi et al. 2019; Emami et al. 2018). They resemble biological membrane and can accommodate both hydrophilic

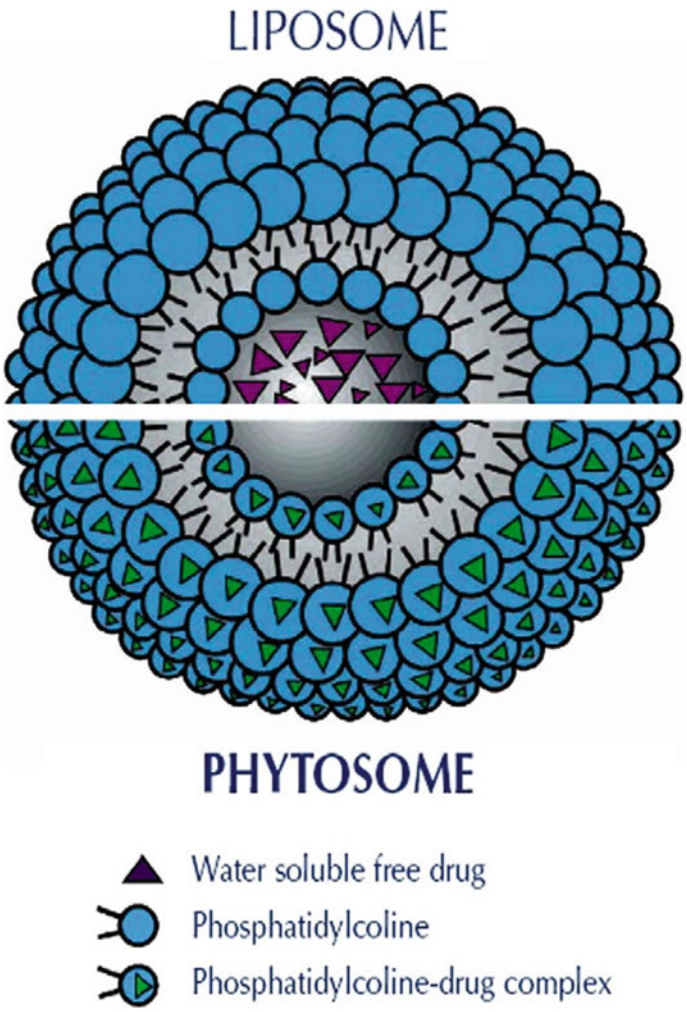

Fig. 20.3 Major difference between liposome and phytosome® (Reproduced with permission from *Selmaty* et al. 2010, Copyright © Elsevier Science BV 2009)

and hydrophobic drugs within their layers which make them unique carrier for drug delivery. In spite of their advantages, successful delivery of liposomes through oral route has always been a challenge as the question remains whether they would remain stable along the GI tract conditions (Park et al. 2011). However, the effective delivery of phytochemicals through oral route has been demonstrated in animal models (Yi et al. 2013). *Flammulina velutipes* sterols was orally delivered through liposomes in Kunming mice and relative bioavailability of ergosterol and 22,23- dihydroergosterol at 162.9 and 244.2%, respectively, was obtained. The sterols, however, was rapidly eliminated within 4 h. A faster and better absorption

of curcumin was also reported when it was encapsulated in leicithin-based liposome exhibiting improved oral bioavailability in animal model (Takahashi et al. 2009). Formulating the *Curcuma longa* (Ukon) extract (LUE) into liposomes was found to deliver better protection against carbon tetrachloride-induced liver injury as compared to the uncapsulated extract (Takahashi et al. 2008). Liposomes are also adaptable to functionalization with targeting ligands to improve their effectiveness in cancer therapy. *Kappaphycus alvarezii* extract containing multi-bioactive compounds was encapsulated into PEGylated-liposome and then functionalized with folic acid to target folate positive breast cancer cells (MCF-7) (Baskararaj et al. 2020). The constructed liposome was highly stable in the physiological buffers with steady drug release and also exhibit cytotoxicity toward MCF-7 in a concentration-dependent manner.

Liposomal formulation also contributes to the improvement in physicochemical properties of natural bioactive compounds such as solubility and stability. Chemical stability of resveratrol was enhanced by liposomes and along with 3-oxo-C_{12}-homoserine lactone, about 70% inhibition of tumor growth in murine tumor model was reported when they are administered intravenously (Coimbra et al. 2011). Encapsulation of enriched-phenolic fraction of the extract from *Pistacia vera* L into nanoliposome exhibits multiple bioactivity including antioxidant, anti-inflammatory, and anti-melanogenic activities making it a promising cosmeceutical preparation for skin pigmentation disorders (Oskoueian et al. 2020). Promotion of stability and enhancement in bioactivity of quercetin (Hao et al. 2017) and bitter gourd (*Momordica charantia*) (Erami et al. 2019) were also reported with their nanoliposomal formulations.

Proliposome systems were also developed with an objective of enhancing the stability and oral bioavailability of the encapsulated drugs. Compared to liposomes, proliposomes are highly stable and obtained in dry, free-flowing particles which form liposomal suspension immediately on contact with water (Yan-yu et al. 2006). Presenting the whole system in the form of solid makes proliposome highly stable while the intrinsic pharmacological properties remain intact.

Phytosomes are complex of phospholipid with herbal extracts developed to enhance the oral bioavailability of natural bioactive compounds. It is a patented technology developed in Italy around 1989 and several phytosome products are already available in the market (Pachuau 2019). The complexation of phosphatidylcholine (phospholipid) with polyphenols in phytosomes led to the formation of intermolecular bond between these two and the amphiphilic nature of the phosphatidylcholine promotes the miscibility of the complex with aqueous and lipid solvents which guide the polyphenol to permeate the lipid-based GI tract lumen (Kidd 2009). Delivery of polyphenols in the form of phytosomes has the capacity to enhance the oral bioavailability of polyphenols at least by 2–6 times (Ajazuddin and Saraf 2010; Kidd 2009). The ratio of the bioactive compounds to the phosphatidylcholine has been considered to be important factor in phytosome formulations. This bioactive compound:phospholipid ratio may range from 0.5:1 to 3:1 and the optimum ratio may depend on the kind of phytochemicals being complexed (Pachuau 2019). Frequently, a combination of bioactive phytochemicals has been

incorporated into phytosomes to attain their synergistic effects (Rathee and Kamboj 2018; Sharma and Sahu 2016).

20.3.2.4 Self-emulsifying Systems

Both micro- and nano-self-emulsifying systems are capable of enhancing oral bioavailability of poorly aqueous-soluble drugs by enhancing their solubility and dissolution rate. They are composed of a lipid, surfactant, bioactive compound, and a co-surfactant, and following oral administration, they swiftly form microemulsions with particle size less than 100 nm within the GI fluid bringing the drug into solution for enhanced absorption (Cui et al. 2009; Dwivedi et al. 2014). Micro- and nano-self-emulsifying systems have been demonstrated to enhance the oral bioavailability of various phytochemicals including curcumin (Cui et al. 2009), arteether (Dwivedi et al. 2014), silymarin (Li et al. 2010; Wu et al. 2006), curcumin, and thymoquinone (Alwadei et al. 2019), naringenin (Khan et al. 2015) as well as plant extracts (Arun and Maneesh 2016).

20.3.2.5 Niosomes

Niosomes are self-assembled non-ionic surfactant vesicles analogous to phospholipid vesicles of liposomes where hydrophilic drugs are encapsulated and hydrophobic drugs are partitioned into the hydrophobic tails of the non-ionic surfactant (Hu and Rhodes 1999; Uchegbu and Vyas 1998). Niosomes are more stable than liposomes and are more economical to prepare from a wide range of surfactants which make them an attractive alternative to liposomes (Song et al. 2015). Niosomal preparations are reportedly initiated from the cosmetic industry in the 1970s and gradually expanded toward drug delivery applications including phytochemicals (Muzzalupo and Mazzotta 2019). Niosomes of poorly soluble D-limonene were reported to prolong the release of D-limonene and its cytotoxicity toward HepG2, Macf-7, and A549 cancer cells was significantly enhanced (Hajizadeh et al. 2019). Niosome also facilitates the solubilization of Lawsone and compared to free Lawsone solution, the antitumor activity of Lawsone noisome against MCF-7 breast cancer cells was increased significantly (Barani et al. 2018).

Studies have shown that niosomes are also effective carrier for the delivery of bioactive phytochemicals across the skin. Compared to their solutions, more efficient delivery of ellagic acid across the human epidermis and dermis was observed when it was formulated as niosomes and this penetration of the skin was reported to be dependent on the vesicle size (Junyaprasert et al. 2012).

Niosomes may suffer from the issue of aggregation, fusion, and leakage of the encapsulated bioactive compounds. To alleviate this problem, proniosomes have been prepared which are dry and free-flowing type that spontaneously form niosomes on gentle agitation with hot water. Proniosomes were demonstrated to

increase the oral bioavailability of poorly soluble alkaloid, vinpocetine by about 4- to 4.9-folds (Song et al. 2015).

20.3.2.6 Hydrogels

Hydrogels are hydrophilic three-dimensional polymer networks which can take up large amount of water. They are biodegradable and the three-dimensional network of the hydrogel disintegrates into non-toxic materials with excellent biocompatibility (Akhtar et al. 2016). Hydrogels are prepared from wide ranges of natural and synthetic polymers and can be presented in the various physical forms such as beads, microparticles, nanoparticles, and films and they have become one of the promising encapsulating systems to provide protection to sensitive phytochemicals and for their controlled delivery (Abaee et al. 2017; Gomez-Mascaraque et al. 2016a). The advantages hydrogels offer in encapsulation of bioactive compounds include the following:

(i) Enhancing stability and bioacessibility of sensitive, poorly aqueous-soluble bioactive molecules (Gomez-Mascaraque et al. 2016a; Han et al. 2020; Zhang et al. 2016).
(ii) pH-dependent and controlled release of bioactive compounds (Bourbon et al. 2016; Lopez Cordoba et al. 2013; Rutz et al. 2013).
(iii) Efficient encapsulation of both hydrophilic and hydrophobic bioactive compounds (Bourbon et al. 2016).
(iv) Enhancing bioactivity (Chan et al. 2010).
(v) Improving bioavailability (McClements 2017).
(vi) High drug-loading capacity due to their large spacing within the polymeric network (Teng et al. 2015).

Various hybrid hydrogel systems such as emulsion hydrogels, organogels and bigels have also been evaluated for encapsulation of bioactive compounds. Encapsulation of bioactive compounds within these networks can improve their stability, solubility and dispersibility thereby improving their overall bioavailability (Mao et al. 2019). Suitable functionalities such as responsiveness to pH, temperature, enzymes etc. can also be imparted to these hybrid hydrogels to provide the desired release characteristics of the formulation (McClements 2017). In emulsion (O/W) gel systems, the continuous aqueous phase gets solidified or gelled to provide structural integrity and flexibility to the whole system. As a result, it has wide application in functional food industry. Bioactive compounds such as curcumin (Geremias-Andrade et al. 2017), quercetin (Chen et al. 2018), α-tocopherol (Freire et al. 2018) have been delivered through emulsion gel systems with improved stability, bioaccessibility and controlled release. In addition, the structural state of emulsion hydrogels also allows them to be used as an efficient fat-replacement in various food products without affecting their sensory characteristics thereby promoting health benefits to consumers (Pintado et al. 2015, 2016).

20.3.2.7 Electrodynamic Processes

In recent years, electrodynamic encapsulation processes such as electrospraying and electrospinning have received increasing attention as an alternative to the more established and commonly employed techniques such as microencapsulation (Alehosseini et al. 2018; Jacobsen et al. 2018). During electrospraying, the high voltage electrostatic force converts the drug-loaded liquid solutions into fine droplets and gets evaporated during their flight toward the ground electrode (Alehosseini et al. 2018). A high degree of molecular interaction in the sprayed liquid produces electrospun fibers, while lower degree of interaction results in electrosprayed particles (Fig. 20.4). In conventional spray-drying process, drugs or bioactive compounds are exposed to high temperature in the range of 170–220 °C to dry and encapsulate the material and this condition of drying may degrade thermolabile drug substances (Jacobsen et al. 2018). However, in electrospraying, exposure to such high temperature has been eliminated which makes it more conducive for encapsulation of heat-sensitive compounds. Electrodynamic encapsulation of bioactive compounds also offers the following advantages (Drosou et al. 2017; Ghorani and Tucker 2015; Wen et al. 2017a; Wen et al. 2017b):

(i) It is a relatively simple, cost-effective, and flexible method for fabrication of nanomaterials.
(ii) It has the potential to scale up to large-scale manufacturing.
(iii) The method is adaptable to wide range of encapsulating materials.

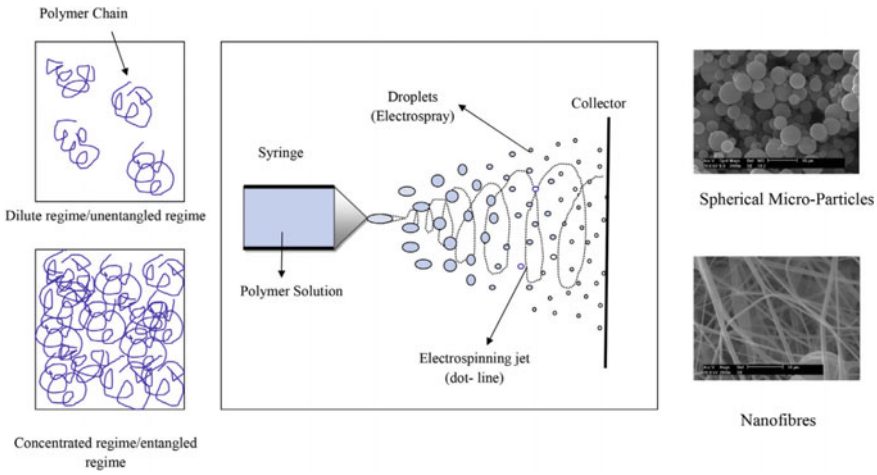

Fig. 20.4 Left: Schematic of physical representation at the molecular level of entanglement regimes for dilute and concentrated polymer concentration. Middle: Schematic diagram of a basic electrospinning (jet formation) and electrospraying (liquid-droplet atomization) processes. Right: Examples of SEM image of microspheres (electrospraying) and nanofibers (Electrospinning) (Reproduced with permission from Ghorani and Tucker 2015, Copyright © Elsevier Science BV 2015)

(iv) Enhanced stability of bioactive compounds.
(v) High surface-to-volume ratio of the nanoscale materials results in better bioavailability.
(vi) Both hydrophilic and hydrophobic bioactive compounds can be encapsulated.

Electrospraying was employed to successfully encapsulate β-carotene in its solubilized form to enhance its stability and also to improve its bioavailability (Basar et al. 2020). When exposed under UV light, the free-β-carotene degrades within 180 min while only 20% degradation was found with the encapsulated β-carotene. Wide ranges of polymers are adaptable to electrodynamic processing including polysaccharides cellulose and its derivatives, guar gum, pectin, starch, chitosan, alginate, etc. (Wen et al. 2017b). Viscosity, surface tension, and electrical conductivity of the polymeric solution were found to influence the morphology of the electrosprayed capsules or fibers (Gomez-Mascaraque et al. 2016b).

20.3.2.8 Solid Dispersion and Micelles

Solid dispersion technique is one of the most commonly employed methods to improve the solubility and bioavailability of poorly aqueous-soluble drugs. Crystalline drugs often exhibit poor solubility in aqueous-based solvents as the lattice energy must be overcome to bring them into solution (Li et al. 2013). Formulation into amorphous solid dispersion helps solubilization of such crystalline drugs as the encapsulating polymers in the solid dispersions trapped them in the amorphous state which facilitates their dissolution once they come in contact with the aqueous solvents. Various cellulose derivatives have been reported to exhibit strong enhancement of curcumin dissolution while also protecting from chemical degradation and affecting pH-dependent release (Li et al. 2013). Various formulations of curcumin such as nanocrystal solid dispersion prepared with hydroxypropyl cellulose SL (CSD-Cur), amorphous solid dispersion with hydroxypropyl methylcellulose acetate succinate (ASD-Cur), and nanoemulsion (NE-Cur) were prepared and the increase in oral bioavailability compared to the unformulated curcumin was reported to be 12-folds for ASD-Cur, 16-folds for CSD-Cur and, 9-folds for NE-Cur (Onoue et al. 2010).

Self-assembled colloidal dispersion of amphiphilic surfactants, also known as micelles, has been another important technique to enhance the solubility of hydrophobic drugs. Certain amphiphilic polymers are also known to form micelles and are known as polymeric micelles (Husseini and Pitt 2008). Polymeric micelles have been shown to enhance the solubility and bioactivity of bioactive compounds. When Pluronic P123- and Solutol HS15-based polymeric micelles were prepared loaded with naringenin, sustained release of naringerin and significant enhancement in its cytotoxicity against cancer cell line were observed (Zhai et al. 2013). Oral bioavailability of paclitaxel in glycyrrhizic acid micelle was also found to enhance sixfolds as compared to Taxol (Yang et al. 2015).

20.4 Conclusion

Enhancement in stability and bioavailability of phytochemicals has been one of the most important challenges in their effective utilization. Thousands of bioactive compounds have been isolated and characterized over the years; however, their therapeutic effectiveness in vivo is often limited by their poor physicochemical properties and modest oral absorption. Several studies have demonstrated that encapsulation into various micro-and nanoplatforms is capable of alleviating such obstacle. Microencapsulation techniques have been proven and commonly employed method for such enhancement. Novel techniques like hydrogels and their variants such as emulsion gels, organo gels, and bigels along with electrodynamic processes like electrospraying and electrospinning techniques are certainly promising approaches to facilitate the effective delivery of these bioactive compounds.

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