Protein–Polysaccharide Complexes (Conjugates) as Delivery Systems

Subjects: Others
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Due to their combination of featured properties, protein and polysaccharide-based carriers show promising potential in food bioactive ingredient encapsulation, protection, and delivery. The common types of protein–polysaccharide complex/conjugate-based bioactive ingredient delivery systems include emulsion (conventional emulsion, nanoemulsion, multiple emulsion, multilayered emulsion, and Pickering emulsion), microcapsule, hydrogel, and nanoparticle-based delivery systems. This entry highlights the applications of protein–polysaccharide-based delivery vehicles in common bioactive ingredients including polyphenols, food proteins, bioactive peptides, carotenoids, vitamins, and minerals. The loaded food bioactive ingredients exhibited enhanced physicochemical stability, bioaccessibility, and sustained release in simulated gastrointestinal digestion.

Keywords: polyphenol ; food protein ; bioactive peptide ; carotenoid ; vitamin ; mineral ; physicochemical stability ; bioaccessibility ; sustained release

1. Polyphenols

Polyphenols have been simply classified into flavonoids and non-flavonoids [1]. A wide range of flavonoid-type polyphenolic compounds, such as anthocyanin [2][3], quercetin [4][5], isoquercetin [6], quercetagetin [7], epigallocatechin gallate [8], and curcumin [9], have been successfully encapsulated into different protein–polysaccharide-based carriers for protection, sustained release, and delivery.

Curcumin is often used as the model of hydrophobic bioactive compounds when designing and fabricating novel delivery systems.

1.1. Curcumin

Curcumin, also called diferuloylmethane, is a natural polyphenolic compound present in the rhizome of *Curcuma longa* (turmeric) and in other *Curcuma* spp. [10]. Due to its wide range of health-promoting activities, such as antimutagenic, antimicrobial, anti-inflammatory, and antioxidant activities, curcumin has strong potential to be applied as a functional food ingredient and nutraceutical [11]. However, curcumin has poor water solubility, low stability, and limited bioavailability, which restrict its application in the food industry. Substantial research efforts have been made to develop food-grade curcumin delivery vehicles in order to overcome the challenges and effectively deliver curcumin in targeted physiological sites [11]. Different types of curcumin delivery systems have been fabricated using protein–polysaccharide conjugates or complexes as building blocks, including core-shell nanoparticle, composite nanoparticle, microcapsule, emulsion, and hydrogel-based delivery systems.

In the past decade, a wide range of protein–polysaccharide complexes have been designed to fabricate core-shell nanoparticles for curcumin delivery, such as casein–soy polysaccharide [12], pea protein–carboxymethylated corn fiber gum [13], cationized gelatin and sodium alginate [14], insect protein–chitosan [15], native and succinylated pea protein–chitosan [16], whey protein–gum arabic [17], and soybean protein isolate–fucoidan complexes [9]. Encapsulation efficiencies of curcumin in these developed core-shell nanoparticles ranged from 30–99% [13][15][17]. The curcumin-loaded casein–soy polysaccharide nanoparticles showed long-term dispersion stability after 30 days of storage at 25 °C [12]. Likewise, the chemical, thermal, and photo stabilities of encapsulated curcumin have been significantly improved. Specifically, lysozyme–*A. Sphaerocephala Krasch* polysaccharide complex nanoparticles increased curcumin stability at physiological pH in aqueous buffer [18]. Approximate 75% of free curcumin degraded in phosphate buffer within 6 min, while 59% and 46% of encapsulated curcumin remained stable after 24 h and 48 h incubation, respectively [18]. Compared to free curcumin (15%), curcumin-loaded pea protein–carboxymethylated corn fiber gum nanoparticles showed a significantly higher thermal stability (95%) after heat treatment (80 °C, 30 min, pH 3.5) [13]. Regarding photo stability, it was reported

that after 90 min of UV radiation, the residual levels of curcumin in the free and nanoencapsulated forms (pea protein isolate–high methoxyl pectin complexes) were 4% and 34%, respectively [19]. In addition, the release profile and oral bioavailability of encapsulated curcumin are of great significance for achieving its health-promoting activities. The release kinetics of curcumin from insect protein–chitosan nanoparticles were determined under the simulated oral, gastric, and intestinal conditions [15]. More than 90% of encapsulated curcumin was released after the simulated digestion process, including 6.3% in oral phase, 8.2% in gastric phase, and 78.1% in intestinal phase. A recent study demonstrated that the oral bioavailability of curcumin loaded in casein–soy polysaccharide complexes increased 3.4-fold in blood of mice compared to the curcumin/Tween 20 treatment [12]. Furthermore, encapsulated curcumin in core-shell nanoparticles showed better antioxidant and anticancer activities in vitro compared to free curcumin [18][13][14][17].

Likewise, encapsulation of curcumin in protein–polysaccharide composite nanoparticles has gained significant research attention. The possible encapsulation mechanism of these nanoparticles is that the formation of protein–polysaccharide complexes results in protein unfolding and exposure of the hydrophobic pockets, which facilitate curcumin binding to the protein moiety of complexes via hydrophobic interactions [20]. Encapsulation efficiencies of curcumin in composite nanoparticles are usually higher than 80% [21][22]. Moreover, curcumin-encapsulated composite nanoparticles have shown great potential in food applications owing to their high dispersion stability and color stability [23]. For example, curcumin-loaded composite nanoparticles (whey protein isolate–sodium alginate nanocomplex) possessed acceptable dispersion stability (no obvious precipitates) in model food processing and storage conditions, such as high concentrations of sucrose and NaCl, and heat treatment at 90 °C for 2 h [24]. Composite nanoparticles effectively provided curcumin protection against light and different pH [20][24][25]. A sustained release of curcumin from composite nanoparticles has been observed in simulated gastric and intestinal fluids, which led to enhanced bioaccessibility of curcumin [25]. Taking the curcumin-loaded zein–fucoidan nanoparticle as an example, the cumulative release rates of curcumin were 10% and 62% in simulated gastric fluid (90 min) and simulated intestinal fluid (240 min), respectively [21]. Many studies have demonstrated that the in vitro antioxidant activities of curcumin in composite nanoparticles were remarkably improved [24][26].

Besides nanoparticle-based delivery systems, curcumin has been successfully loaded in other types of protein–polysaccharide delivery vehicles, such as oil-in-water emulsions [27][28], microcapsules [29], and hydrogels [30]. Specifically, the curcumin loading efficiency of nanoemulsion stabilized by casein–soy soluble polysaccharide complexes was as high as 99.9% and only 3% of the loaded curcumin degraded during storage at 4 °C for 40 days [27]. A controlled release of curcumin from the nanoemulsion was achieved during simulated gastrointestinal digestion and an 11-fold increase in curcumin oral bioavailability in mice was observed [27]. Likewise, nanoemulsion with Maillard-type bovine serum albumin–dextran conjugates was fabricated for protection and oral delivery of curcumin [28]. When curcumin was encapsulated in spray-dried microcapsules fabricated with whey protein–maltodextrin and gum arabic, it became resistant to in vitro gastric digestion but was released in simulated intestinal fluids [29]. Recently, Su et al [30]. developed a β-lactoglobulin–propylene glycol alginate-based hydrogel for co-delivery of curcumin and probiotics. Besides protection of probiotics, the encapsulated curcumin had a sustained release in simulated gastrointestinal tract conditions and exhibited good stability when exposed to light and during long-term storage [30].

1.2. Resveratrol

Resveratrol is a non-flavonoid polyphenol with numerous health promoting properties, such as antioxidant, anti-inflammatory, anti-proliferative, anticancer, and anti-aging activities [31]. Nonetheless, utilization of resveratrol as a nutraceutical or functional food ingredient is challenged by its poor water solubility, chemical instability, and low bioavailability [31]. To address these issues, distinct types of protein–polysaccharide-based delivery systems, such as core-shell nanoparticles, oil-in-water emulsions, and multilayered emulsions, have been developed [32][33][34].

When resveratrol was loaded into core-shell nanoparticles, the encapsulation efficiencies often ranged from 50% to 90% [35][36]. It was reported that 28/40 dual-frequency ultrasound effectively increased the encapsulation efficiency of resveratrol in zein–chitosan complex nanoparticles from 51% to 65% [36]. After encapsulation, resveratrol lost its crystalline structure and changed to the amorphous form in alginate/chitosan–zein nanoparticles and α-lactalbumin–chitosan nanoparticles [37][32]. The major driving forces between resveratrol and α-lactalbumin–chitosan nanoparticles include hydrophobic interaction and hydrogen bonding [37]. Light, heat, and storage stabilities of encapsulated resveratrol in core-shell nanoparticles were remarkably increased compared to those of free resveratrol. For example, after exposure to UV light for 200 min and heat treatment at 85 °C for 300 min, the retention rates of free and encapsulated resveratrol in α-lactalbumin–chitosan nanoparticles were 44% and 47%, and 85% and 86%, respectively [37]. Moreover, sustained in vitro release of resveratrol from nanoparticles in simulated gastrointestinal digestion could be enhanced. For instance, in simulated gastric phase, 77% of free resveratrol was released compared to 52% released from resveratrol encapsulated

in zein nanoparticles [32]. A recent study evidently demonstrated that compared to free resveratrol, the in vitro bioaccessibility of encapsulated resveratrol in hollow zein–chitosan nanoparticles increased 2-fold from 44% to 90% [35]. Consequently, in vitro antioxidant and anticancer activities of the encapsulated resveratrol were improved as well [37][31]. However, there is a dearth of information on the oral bioavailability and in vivo bioactivities of encapsulated resveratrol.

It has been reported that when loading a low amount of resveratrol (0.02 g/100 g) into the oil-in-water emulsion stabilized by Maillard-type sodium caseinate–corn starch hydrolysate conjugates, the in vitro antioxidant activity significantly increased [38]. Food-grade protein–polysaccharide multilayered emulsions have also been designed to encapsulate and protect resveratrol and to increase its antioxidant activity [33]. Lactoferrin–alginate multilayered emulsions were reported to be stable only at a high concentration of alginate (>0.18% *w*/*w*) owing to the bridging flocculation effect at low alginate concentrations [33]. The antioxidant activity of this resveratrol-loaded multilayered emulsions was maintained during storage for 4 weeks whereas decreased antioxidant activity of free resveratrol was observed in the third week [33].

2. Proteins and Bioactive Peptides

Beyond their nutritional properties, several food proteins and peptides have demonstrated numerous health-promoting properties, such as antihypertensive, antimicrobial, cholesterol-lowering, antithrombotic, anticancer, immunomodulatory, mineral binding, opioid-like, and antioxidant activities [39]. However, the in vitro biological activities of proteins and bioactive peptides do not generally translate into in vivo pharmacological functions in animal studies and human clinical trials [40]. One of the major reasons for this discrepancy is the low biostability or bioaccessibility of proteins and peptides during gastrointestinal digestion, which further results in low bioavailability [41][42]. In addition, bioactive peptides often have a bitter taste and hygroscopicity due to the exposure of hydrophobic and hygroscopic amino acid residues resulting from hydrolysis, which limit their applications in food product development [40]. Protein–polysaccharide-based delivery systems have been developed for protection and controlled release of proteins and bioactive peptides in order to enhance their in vivo bioactivities, and sensory and physicochemical properties. For example, lactoferrin has been trapped in nanocarriers for broadening its applications in food and pharmaceutical industries [43]. The highest encapsulation efficiency of lactoferrin in whey protein isolate–high methoxyl pectin nanoparticles was reported at the optimum condition of 2:1 protein–pectin ratio (*w*/*w*) and pre-acidification at pH 3.5. However, encapsulation efficiency was only 25% at the optimized conditions [43]. In addition to enhancing the encapsulation efficiency, the release profile, stability, and biological activities of encapsulated lactoferrin need to be explored in future studies.

Furthermore, a soybean protein isolate–pectin microcapsule has been designed to encapsulate casein hydrolysates for attenuating the bitter taste and hygroscopicity [44]. The encapsulation efficiency decreased from 92% to 79% when the loading amount of casein hydrolysate increased from 50% to 150% (*w*/*w*). The results showed that encapsulated hydrolysates had lower hygroscopicity and less bitter taste compared to free hydrolysate [44]. Jo and Schaaf [45] recently fabricated food-grade double emulsions ($W_1/O/W_2$) to improve the controlled release of bioactive peptides at different temperatures. The bioactive peptide–polysaccharide complex-loaded double emulsions had encapsulation efficiency of >90% and possessed a higher heat stability. Controlled release of encapsulated bioactive peptide from the double emulsions was observed at 45 °C (<1%) and 65 °C (<30%) during storage for 4 h. Oil types played notable roles in the peptide release from the double emulsions. More rapid release of the peptide was observed for double emulsions containing oil with medium chain triglycerides, e.g., coconut oil, compared to oil with long chain triglycerides, e.g., canola oil [45].

3. Carotenoids

Carotenoids are natural pigments in various fruits and vegetables, which have many human health benefits, such as antioxidant, intercellular communication, and immune system activities. Carotenoids can be classified into two groups on the basis of their chemical structures, including xanthophylls (e.g., lutein) and carotenes (e.g., β-carotene and lycopene) [46]. It is challenging to utilize carotenoids as natural colorants in food products due to their low water solubility and chemical instability. Encapsulation in protein–polysaccharide systems is a suitable approach to overcome this barrier.

3.1. Lutein

Core-shell nanoparticle-based carriers are widely investigated for encapsulation and oral delivery of lutein [47]. For example, compared to lutein-loaded protein nanoparticles, modified rice protein–carboxymethylcellulose nanoparticles efficiently controlled the release of lutein during gastrointestinal digestion, effectively inhibited the proliferation of breast cancer cells, and increased the lutein uptake rate and absorption [47]. Nonetheless, proteins also play essential roles in the formation of core-shell nanoparticles for lutein delivery. It was suggested that a high mass ratio of protein–lutein

increased encapsulation efficiency. The encapsulation efficiency of lutein in zein–soluble soybean polysaccharide nanoparticles was higher than 80% when the mass ratio of zein–lutein was 25:1. However, encapsulation efficiency was only 35% at the mass ratio of 10:1 [48]. Bioaccessibility of the encapsulated lutein was two times higher than that of free lutein [48]. To increase the stability of lutein carriers, the formation parameters of whey protein isolate–pectin nanoparticles (protein–polysaccharide ratio, pH, and type of pectin) have been optimized. The most stable system was established with low methoxyl pectin at a protein–polysaccharide ratio of 4:1 and pH 5.0; the carrier remained stable after storage for 30 days [49].

Oil-in-water emulsions are another common type of lutein delivery system with good stability, which can be emulsified by both Maillard-type protein–polysaccharide conjugates and electrostatic complexes [50][51]. Specifically, lutein-loaded emulsions stabilized by casein–dextrin conjugates were reported to be stable at a wide range of pH values (from 3 to 7) and not aggregate during simulated gastric digestion; this was attributed to the steric repulsion resulting from the dextran [50]. Moreover, lutein-enriched emulsions stabilized by egg yolk-modified starch complexes, especially egg yolk–hydroxypropyl distarch phosphate complexes, showed good physical stability, low lipid oxidation, and high lutein retention during storage at 37 °C [51].

Lutein has also been encapsulated in Pickering emulsions stabilized by β-lactoglobulin–gum arabic-based nanoparticles. The nanoparticles exhibited a core-shell structure and significantly contributed to the stability of the Pickering emulsions. The formed emulsions showed a high resistance against flocculation and coalescence and favorable storage stability. After 12 weeks of storage, more than 90% of encapsulated lutein was retained in the Pickering emulsions [52].

3.2. β-Carotene

Due to the antioxidant and pro-vitamin A nature of β-carotene, many attempts have been made to develop delivery systems to enhance its dispersant state, chemical stability, bioavailability, and functionalities. By and large, O/W emulsions are effective for the protection and delivery of β-carotene [53][54]. O/W emulsion-based β-carotene delivery systems are commonly stabilized by Maillard-type protein–polysaccharide conjugates [53][55][56][54]. The increased emulsifying activity of protein–polysaccharide (e.g., soy protein isolate–*Pleurotus eryngii* polysaccharide) conjugates was attributed to their decreased surface hydrophobicity and flat surface morphology [55]. A recent study demonstrated that ovalbumin–dextran conjugates possessed good emulsifying stability in different environmental conditions, including pH (3.0–10.0), high ionic strength (150 mM NaCl), and thermal treatment (90 °C for 30 min) [54]. Bioaccessibility of encapsulated β-carotene in O/W emulsions stabilized by deamidated wheat gluten–maltodextrin conjugates was close to 60% [53]. The enhanced bioaccessibility favorably contributed to the increased antioxidant activity of β-carotene in Caco-2 intestinal cells [55][56].

β-carotene has been successfully entrapped in O/W nanoemulsions stabilized by whey protein hydrolysate–pectin soluble complexes and the concentration of β-carotene was considered as a critical parameter [57]. Average droplet size of the nanoemulsion was ~95 nm, and encapsulation efficiency was as high as 92% when the concentration of β-carotene was 25 mg/100 g emulsion. However, when the concentration of β-carotene increased to 75 mg/100 g emulsion, the nanoemulsion displayed a larger droplet size (127 nm) and a significantly lower encapsulation efficiency (27%). Additionally, lower concentration of loaded β-carotene increased nanoemulsion stability against droplet coalescence and retarded the loss of antioxidant activity of β-carotene during storage [57]. Moreover, Yi et al. [58] designed high-internal phase Pickering emulsions stabilized by pea protein–high methoxyl pectin colloidal particles as novel β-carotene delivery systems. The spherical protein–polysaccharide colloidal particles were formed spontaneously by electrostatic interaction. The fabricated β-carotene-loaded Pickering emulsions displayed high stability against pH variation. However, bioaccessibility of the encapsulated β-carotene in Pickering emulsions was only 26% [58], which needs to be improved if intended to be used in practical food applications.

3.3. Lycopene

Due to its highly unsaturated structure, lycopene is sensitive to heat and light, which may result in oxidation and isomerization [59]. Protein–polysaccharide-based microcapsules have been fabricated to encapsulate lycopene [59]. When gelatin–pectin complexes were utilized as the wall materials, encapsulation efficiency of lycopene was higher than 90%. However, this microcapsule-based delivery system did not provide effective protection for lycopene during storage, with degradation rate of 14% per week [59]. When Maillard-type whey protein isolate–xylo-oilgosaccharide conjugates were applied as wall materials, storage stability of the encapsulated lycopene was improved. The degradation rates of lycopene after storage for 36 days at 4, 25, and 40 °C were 12%, 54%, and 60%, respectively. Meanwhile, the microcapsules based on protein–polysaccharide conjugates resulted in high encapsulation efficiency (94%) and lycopene solubility (92 g/L). Compared to free lycopene, bioaccessibility of the encapsulated lycopene significantly increased from 16% to 60%.

Hence, whey protein isolate–xylo-oilgosaccharide conjugate-based microcapsules are considered as promising lycopene delivery systems [60].

4. Vitamins

Vitamins are defined as a group of essential micronutrients that cannot be synthesized by the human body; they are classified into fat-soluble (A, D, E, and K) and water-soluble vitamins (e.g., folic acid) [61]. Deficiency of vitamins can result in severe diseases, such as scurvy and night blindness [61]. Vitamins can easily be degraded during food processing and storage since they are chemically reactive and sensitive to environmental factors such as light, pH, temperature, and oxygen [61]. It is well established that microencapsulation and nanoencapsulation prevent vitamin loss during food processing and storage, and help to achieve targeted delivery and sustained release [61][62]. However, limited research has been conducted to date on development of protein–polysaccharide-based vitamin delivery systems. Most existing research has particularly focused on folic acid and vitamin D_3 delivery.

To improve the stability and controlled delivery of folic acid, soy protein–soy polysaccharide complex nanogels were developed [63]. The folic acid-loaded nanogels possessed good water dispersibility in acidic conditions due to the presence of a polysaccharide surface. More importantly, the nanogels provided strong protection of folic acid from heat, oxygen, and light in acidic conditions, whereas the encapsulated folic acid showed a rapid release at neutral pH value [63]. Another study prepared and optimized stable $W_1/O/W_2$ whey protein–maltodextrin double emulsions for folic acid encapsulation by the low-energy emulsification technique [64]. The folic acid-encapsulated nanoemulsions showed potential for utilization in fortification of liquid foods but limited applications in solid foods [64]. To address this drawback, a spray drying technique was used to prepare folic acid-incorporated whey protein–pectin nanoparticles, which led to the lowest release rate of folic acid at pH 4 and highest release at pH 11 [65].

Vitamin D_3 is a lipid-soluble compound that easily degrades under acidic conditions. Ovalbumin–pectin nanocomplexes were developed as effective carriers for vitamin D_3 with encapsulation efficiency of 96%. Encapsulation of vitamin D_3 in the nanocomplexes was driven by electrostatic interactions, hydrogen bonding, and hydrophobic interactions. In vitro release study indicated that only 11% of loaded vitamin D_3 was released from the nanocomplexes in simulated gastric fluid within 60 min, whereas in simulated intestinal fluid, the cumulative release rate within 120 min reached 98% [66]. Furthermore, it was demonstrated that the addition of sodium alginate significantly enhanced the stability of vitamin D_3-incorporated ovalbumin–pectin nanocomplexes due to the strong negative charge of sodium alginate [67].

5. Mineral (Iron)

Some minerals, such as iron, calcium, and zinc, play important biological roles and are essential micronutrients for maintaining human health. Hence, food fortification with minerals has been considered as one of the most effective strategies for combating micronutrient malnutrition globally. However, mineral fortification can adversely influence the physical and sensory properties of foods, and the absorption and bioavailability of fortified minerals could be impeded by other food components such as phytates [68]. To overcome these challenges, research efforts have led to the development of effective protein–polysaccharide-based carriers for protection and delivery of minerals, especially iron [69][70]. Kazemi-Taskooh and Varidi [69] designed a composite cold-set hydrogel formulated with whey protein isolate and gellan gum as an iron delivery system. The encapsulation efficiency of iron in hydrogel reached 94%, and was affected by total biopolymer concentration, protein/polysaccharide ratio, and iron concentration. However, a majority of the encapsulated iron (up to 89%) was released from the hydrogel in simulated gastric digestion rather than simulated intestinal digestion. This could be because of the cationic net charge of proteins at low acidic pH, resulting in electrostatic repulsion and dissociation of bound iron from the complex. Increase gastric stability and sustained release of iron in the intestinal phase need to be enhanced by modification of the hydrogel structures. On the other hand, nanoparticle-based iron delivery systems, which were fabricated with whey protein isolate and gum arabic, dramatically slowed the release of entrapped iron (only 20% released) in the simulated gastric phase [70].

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