Graphical Abstract:

“Recent progress in hydrogel delivery systems for improving nutraceutical bioavailability” by D.J. McClements

**Recent progress in hydrogel delivery systems for
improving nutraceutical bioavailability**

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Abstract

Nutraceuticals are bioactive molecules found in foods that may improve human performance, wellbeing, or health. The potential health benefits of many nutraceuticals are not fully realized because they are chemically degraded during storage or within the gastrointestinal tract. Consequently, there is a need to develop food-grade delivery systems to encapsulate and protect nutraceuticals until they reach an appropriate location within the human body, *e.g.*, mouth, stomach, small intestine, or colon. Hydrogel beads (“microgels”) assembled from proteins and/or polysaccharides can improve nutraceutical performance by protecting them from chemical degradation. These beads can be fabricated using simple and inexpensive processing operations that typically involve two steps: (i) formation of biopolymer-enriched particles; (ii) cross-linking of the biopolymers. Hydrophilic nutraceuticals are usually mixed directly with the biopolymer solution prior to formation of the hydrogel beads, whereas hydrophobic nutraceuticals are typically incorporated into lipid droplets (emulsions or nanoemulsions) prior to mixing with the biopolymer solution. Common particle-formation methods include injection, shearing, templating, and phase separation, whereas common cross-linking methods include changes in solvent quality, counter-ion addition, heating, and cooling. This article provides an overview of recent progress in the design and fabrication of food-grade hydrogel beads to encapsulate and protect nutraceuticals, including some examples of their potential applications.

Keywords: Hydrogel beads; microgels; nanoemulsions; gastrointestinal tract; nutraceuticals; targeted release

1. Introduction

There has been considerable interest in the identification, isolation, and characterization of bioactive agents from natural edible sources that may be beneficial to human health, wellbeing, and performance (Espin, Garcia-Conesa, & Tomas-Barberan, 2007; Herrero, Cifuentes, & Ibanez, 2006; Wildman & Kelley, 2007). These “nutraceuticals” vary considerably in their biological origin, molecular properties, physicochemical characteristics, and biological activities. Some widely studied nutraceuticals are ω -3 polyunsaturated lipids, conjugated linoleic acid (CLA), phytosterols, carotenoids, and polyphenols (Abuajah, Ogbonna, & Osuji, 2015; McClements, Decker, Park, & Weiss, 2009; Wildman, et al., 2007). Some of these nutraceuticals have relatively good solubility, stability, and bioavailability characteristics and so can simply be directly incorporated into foods. On the other hand, the efficacy of many nutraceuticals is limited because of their poor solubility characteristics, low chemical stability, and low bioavailability (Huang, Yu, & Ru, 2010; McClements, et al., 2009; Velikov & Pelan, 2008). There has therefore been considerable interest in the development of food-grade delivery systems to encapsulate, protect, and release nutraceuticals at the appropriate site of action within the human body (Kimpel & Schmitt, 2015; McClements, 2015; Shin, Kim, & Park, 2015).

The focus of this review article is on recent advances in the design, fabrication, and characterization of hydrogel beads to encapsulate nutraceuticals. The main constituents used to form hydrogel beads in the food industry are biopolymers: proteins and polysaccharides (Dickinson, 2012; Jones & McClements, 2010; McClements & Li, 2010; Schmitt, et al., 2010; Wang, Bamdad, Song, & Chen, 2012). Typically, a solution containing a mixture of nutraceuticals and biopolymers is first used to form a small particle, and then the biopolymer molecules within the particle are cross-linked to form nutraceutical-loaded hydrogel beads. The hydrogel beads formed may vary in their compositions, dimensions, and structures, which leads to variations in their physicochemical properties and functional performances (Joye & McClements, 2014b; Shewan & Stokes, 2013; Zhang, Zhang, Chen, Tong, & McClements, 2015a). This article provides a brief overview of hydrogel bead fabrication methods, the properties of hydrogel beads that can be tailored to attain different functional attributes, and some

recent examples of the application of hydrogel beads to encapsulate, protect, and release nutraceuticals.

2. Hydrogel bead formation

Typically, the formation of nutraceutical-loaded hydrogel beads is a two-step process (**Figure 1**). First, a solution containing a mixture of nutraceuticals and biopolymers is made to form one or more small particles (usually in the range 100 nm to 1000 μ m). Second, the biopolymer molecules within the small particles are cross-linked with each other using an appropriate method leading to the formation of a hydrogel matrix within the beads. The nature of the particle-formation and particle-gelation methods used depends on the precise method used to fabricate the hydrogel beads (Matalanis, Jones, & McClements, 2011; Shewan, et al., 2013). A brief summary of some of the methods that have been explored for their potential application in the food industry are given below. More details about the different methods can be found in more comprehensive recent review articles (Joye & McClements, 2014a; Shewan, et al., 2013; Zhang, et al., 2015a).

2.1. Injection

In this case, small aliquots of a nutraceutical-biopolymer solution are injected into another solution that promotes biopolymer gelation (**Figure 2**). The gelling solution may contain specific components that promote cross-linking of the biopolymer chains, *e.g.*, mineral ions, acids, bases, or enzymes. For example, anionic polysaccharides (such as alginate, pectin, and carrageenan) and proteins (such as caseins above their isoelectric point) are commonly cross-linked by including multivalent cations (such as calcium) in the gelling solution. Proteins (such as casein and whey protein) can often be enzymatically cross-linked using transglutaminase, whereas some polysaccharides (such as beet pectin) can be enzymatically cross-linked using laccase (Guo, Zhang, & Yang, 2012; Zeeb, Fischer, & Weiss, 2014). Alternatively, the temperature of the gelling solution can be controlled to promote hot-set or cold-set gelation of certain biopolymers. This approach can be used to form gelatin hydrogel beads by injecting a hot-gelatin solution into a cold environment. At high temperatures the gelatin molecules have a random coil conformation, but upon cooling below a critical temperature they form helical regions acts as cross-links between different molecules through hydrogen bonding

(Karim & Bhat, 2008). Conversely, globular proteins (such as those from whey, egg, or soy) can be made to gel by heating them above their thermal denaturation temperature to cause them to unfold and associate through hydrophobic attraction and disulfide bond formation (Foegeding, 2006). The injection approach has been used to form calcium alginate beads containing functional lipid droplets that protect them from digestion within the upper gastrointestinal tract (Li, Hu, Du, Xiao, & McClements, 2011a). Hydrogel beads formed using this approach have also been used to encapsulate and protect insulin (Silva, Ribeiro, Figueiredo, Goncalves, & Veiga, 2006), thyme oil (Stojanovic, et al., 2012), flavors (Petzold, et al., 2014) and curcumin (Zeeb, Saberi, Weiss, & McClements, 2015). Hydrogel beads with a variety of different structures, dimensions, and functional properties can be created using alginate beads (Leong, et al., 2016).

2.2. Emulsion Templating

In this method, a nutraceutical-biopolymer solution is homogenized with an oil phase that contains an oil-soluble surfactant so as to form a water-in-oil (W/O) emulsion (**Figure 2**) (Liu, Wang, Gao, Liu, & Tong, 2008; Sung, Xiao, Decker, & McClements, 2015). This system therefore consists of biopolymer-rich water droplets suspended in an oil phase. The system conditions are then changed to gel the biopolymer molecules inside the water droplets. For example, the system could be cooled to gel a cold-setting biopolymer (such as gelatin) or heated to gel a heat-setting biopolymer (such as whey protein). Alternatively, chemical cross-linking agents could be added that diffuse through the oil phase and into the water droplets where they cross-link the biopolymer chains, such as calcium ions, acids, or bases. Once the hydrogel beads have been formed, they can be removed from the oil phase by centrifugation, filtering, and/or solvent extraction. Some of the major advantages of this approach are that hydrogel beads with well-defined sizes can be produced, and that it is possible to form beads with relatively small dimensions ($< 1 \mu\text{m}$). Recent studies have shown that this approach can be used to encapsulate hydrophobic substances inside of small hydrogel beads (Sung, et al., 2015).

2.3. Electrostatic Complexation

In this case, the nutraceuticals are mixed with a solution that contains two types of biopolymers with different electrical charge characteristics (Chen, Remondetto, &

Subirade, 2006; Li & McClements, 2011b; Schmitt, Sanchez, Desobry-Banon, & Hardy, 1998; Turgeon, Schmitt, & Sanchez, 2007). Under conditions where the two biopolymers have opposite charges they may associate with each other due to electrostatic attraction, which leads to the formation of nutraceutical-loaded biopolymer-rich particles suspended in a biopolymer-depleted aqueous phase. The biopolymer-rich particles can then be made to gel by adding a chemical cross-linking agent or by changing the temperature as described earlier for other methods. These systems are often formed from an ionic polysaccharide and a protein. For example, anionic polysaccharides will tend to form electrostatic complexes with proteins at pH values around and below the isoelectric point where the proteins have appreciable regions of positive charge on their surfaces. These types of electrostatic complexes are highly sensitive to pH and ionic strength since these parameters will influence the strength of the electrostatic attraction. Thus, they tend to dissociate at pH ranges where the sign of the charge on the two biopolymers is similar or at high salt concentrations. Electrostatic complexes of proteins and polysaccharides have been successfully used to encapsulate a number of nutraceuticals, including vitamin D (Ron, Zimet, Bargarum, & Livney, 2010), β -carotene, folic acid, and curcumin (Hosseini, Emam-Djomeh, Sabatino, & Van der Meeren, 2015)

2.4. Antisolvent Precipitation

In this case, a nutraceutical-biopolymer solution is prepared using a good solvent, and then this mixture is injected into an antisolvent (Chan & Kwok, 2011; Joye & McClements, 2013; Thorat & Dalvi, 2012). This process causes the biopolymer molecules to associate with each other and form small particles that can trap the nutraceutical molecules inside. It is debatable whether the particles formed by this method can truly be considered to be hydrogel beads, since they typically contain relatively little water. Nevertheless, they do have some similar characteristics to hydrogel beads, since they are both composed of biopolymer molecules that are associated with each other. One advantage of this method is that it is possible to form nutraceutical-loaded biopolymer particles with relatively small sizes ($d < 500$ nm), which may be advantageous for certain applications. This method has commonly been used to form nutraceutical-loaded biopolymer particles consisting of hydrophobic proteins, such as zein or gliadin (Chen, Zheng, McClements, & Xiao, 2014; Davidov-Pardo, Perez-Ciordia,

Marin-Arroyo, & McClements, 2015; Patel & Velikov, 2014; Zou, et al., 2016). In these examples, the nutraceuticals and proteins are both dissolved in a concentrated ethanol solution that is then injected into water, which leads to the spontaneous formation of nutraceutical-loaded protein nanoparticles.

2.5. Thermodynamic incompatibility

In this case, the nutraceuticals are mixed with a solution that contains two types of biopolymers (A and B) that are thermodynamically incompatible, *i.e.*, there is a net repulsive interaction between them (Matalanis, et al., 2011; Schmitt, et al., 1998; Turgeon, et al., 2007). As a result the system separates into two phases, with one phase being rich in biopolymer-A (phase-A) and the other phase being rich in biopolymer-B (phase-B). This system can then be sheared to form a water-in-water (W/W) emulsion consisting of phase-A particles dispersed in phase-B, or *vice versa*. The particles can then be made to gel by adding a chemical cross-linking agent or by changing the temperature depending on the nature of the biopolymers they contain (Norton & Frith, 2001). Alternatively, they can be stabilized by coating them with a layer of additional biopolymers, *e.g.*, by electrostatic deposition.

Hydrophilic nutraceuticals may simply be mixed with an aqueous solution of biopolymers prior to bead formation, however hydrophobic nutraceuticals may have to be encapsulated within small lipid droplets prior to bead formation. This may be achieved by dissolving the nutraceuticals in an oil phase and then forming an oil-in-water emulsion or nanoemulsion. This approach has been used to form hydrogel beads that contain encapsulated ω -3 oils (Matalanis & McClements, 2012).

2.6. Factors affecting selection of formation method

Each of the different methods available for fabricating hydrogel beads has certain advantages and limitations for particular applications. The fabrication methods differ in the size and polydispersity of the beads that can be produced. For example, the minimum diameter of the hydrogel beads that can be produced using emulsion templating or antisolvent precipitation methods (≈ 100 nm) is usually smaller than for electrostatic complexation and thermodynamic incompatibility methods (≈ 1 μ m) and for injection methods (≈ 10 μ m). The fabrication methods also differ in the nature of the materials that

can be used to fabricate the hydrogel beads, *e.g.*, the electrostatic complexation method requires two or more biopolymers that have opposite charges. In addition, there are considerable differences in the cost, throughput, scalability, and ease of implementation, which impact the commercial viability of the different methods. For example, the emulsion templating method can produce small hydrogel beads, but it is time-consuming and laborious, and requires the use of relatively large quantities of oil and organic solvent, which limit its widespread commercial application.

3. Hydrogel bead properties

The functional performance of hydrogel beads for encapsulating, protecting, and releasing nutraceutical agents depends on their composition and structure (Matalanis, et al., 2011; Shewan, et al., 2013). In this section, a brief overview of some of the most important hydrogel bead properties that can be controlled is given, and their relationship to bead performance is highlighted.

3.1. Composition

Hydrogel beads can be constructed from a variety of different types of proteins and polysaccharides depending on the method used, and the functional properties required. These biopolymers differ in the number, type, sequence and bonding of the monomers, which leads to differences in their molecular weight, conformation, polarity, charge, stiffness, and chemistry. In certain applications it is important to control the composition of the hydrogel beads to obtain certain desirable functional attributes. The nature of the biopolymers used to assemble the hydrogel beads will influence the release mechanism of the nutraceuticals, *e.g.*, simple diffusion, swelling, or disintegration (**Figure 4**). Many polysaccharides are dietary fibers and are therefore not degraded within the upper gastrointestinal tract (GIT), *e.g.* alginate, pectin, carrageenan, locust bean gum, and cellulose. These types of biopolymers may therefore be useful when the aim is to design a hydrogel bead that remains intact in certain regions of the upper GIT, but then disintegrates and delivers the nutraceuticals in the colon. Conversely, other types of polysaccharide (*e.g.*, digestible starch) and many proteins are degraded within the upper GIT, and may therefore be useful for developing triggered release mechanisms. Starch-based hydrogels could be used to deliver nutraceuticals to the mouth, whereas protein-

based hydrogels could be used to deliver them to the stomach or small intestine. The composition of a hydrogel bead may also impact the rate of certain types of chemical reactions, *e.g.*, some proteins are effective antioxidants that can inhibit the degradation of nutraceuticals prone to oxidation. Consequently, it may be advantageous to use these proteins in hydrogel beads containing nutraceuticals that are susceptible to oxidation.

3.2. Dimensions

Hydrogel beads vary considerably in their dimensions depending on the nature of the biopolymers and fabrication methods used to prepare them. Typically, the size varies from around a few hundred nanometers (*e.g.*, for antisolvent precipitation, emulsion templating, and electrostatic complexation methods) to a few millimeters (for some injection methods). The size of the beads has a major impact on many of their important physicochemical and functional properties. The optical properties of a suspension of hydrogel beads depends on their size. Light scattering occurs most strongly when the bead dimensions are similar to the wavelength of light, and decreases for smaller and larger bead dimensions. Very small beads ($d < 50$ nm) may lead to a system that is optically transparent, whereas very large beads ($d > 100$ μ m) may be observed by the human eye. The dimensions of the beads may also influence the perceived mouthfeel of a food product: typically beads with diameters greater than about 50 μ m can be perceived as separate particles in the human mouth, which may be undesirable if a smooth texture is required. Bead dimensions also determine the rate at which they will move due to gravity, with the creaming or sedimentation velocity increasing with increasing bead size. Bead dimensions will also influence the retention, protection, and release of any encapsulated nutraceuticals. Typically, the retention rate increases and the release rate decreases as the beads become larger because the diffusion path through the hydrogel matrix increases (Dan, 2016). The stability of components within the hydrogel beads may also improve as the bead size increases, particularly if there are some components in the surrounding aqueous phase that promote nutraceutical degradation. This is because the distance between the nutraceuticals and reaction-promoters increases as the bead size increases.

3.3. Internal Structure

The internal structure of the hydrogel beads depends on the packing of the

biopolymer molecules within the three-dimensional gel network. Food-grade hydrogel beads may be prepared that have very dense internal structures with small pores (such as those fabricated by antisolvent precipitation) or that have very open internal structures with large pores (such as those fabricated by some injection methods). The nature of the pores will have a major impact on the retention, protection, and release of nutraceuticals from hydrogel beads (**Figure 5**). If the encapsulated substances (molecules or particles) are much smaller than the pores, then they will easily diffuse through the hydrogel matrix. Consequently, they will not be retained very well, and they will be susceptible to chemical degradation by any chemical-promoters that can diffuse into the beads. Conversely, if the encapsulated substances are much larger than the pores, then they will not easily diffuse through the beads. Consequently, they will be retained well, and will be better protected from any promoters of chemical degradation. It may therefore be important to carefully control the internal structure of the hydrogel beads depending on the nature of the nutraceutical to be encapsulated. In addition, it may be possible to alter the pore size in response to an external trigger (such as pH, ionic strength, or temperature), so that an encapsulated substance can be released once it reaches a particular environment. For example, a bead may swell under certain pH conditions, thereby increasing its pore size, and releasing encapsulated nutraceuticals. In some cases, hydrogel beads are prepared with a core-shell structure, in which one type of material forms the inner core and another material forms the outer shell. For this type of system, the retention and release depends on the thickness and porosity of the shell (Dan, 2016).

3.4. Physical properties

Hydrogel beads may vary considerably in their physical properties (density, refractive index, and rheology) depending on the type, concentration, and packing of the biopolymers they contain. These differences in physical properties may alter the stability and functional performance of hydrogel beads. For example, the density of a bead will influence its tendency to cream or sediment within an aqueous solution. Typically, biopolymers are denser than water, and so hydrogel beads have a tendency to sediment. Nevertheless, studies have shown that their stability to gravitational separation can be enhanced by incorporating oil droplets (low density) within them so that the overall density matches that of water (Matalanis & McClements, 2013). The refractive index of

a bead will determine its light scattering properties, which will impact the optical properties of the overall system (McClements, 2002). The refractive index typically increases with increasing biopolymer concentration, and so beads that contain densely packed biopolymer molecules will tend to scatter light more strongly than those that contain less densely packed ones. This may be an important consideration for the design of hydrogel beads for applications in food products that are expected to have a particular appearance. The rheology of the hydrogel beads depends on the number and strength of the cross-links between the biopolymer molecules. The rheology of beads may therefore vary considerably: soft to hard; rubbery to brittle; reversible to irreversible. These rheological attributes are important for certain applications since they influence the stability of the hydrogel beads to shrinking or swelling under appropriate solution or environmental conditions (Aktas, Evingur, & Pekcan, 2009; Koetting, Peters, Steichen, & Peppas, 2015; Voo, Ooi, Islam, Tey, & Chan, 2016) or to disruption in the presence of mechanical forces, such as stirring, flow through a pipe, or mastication (Farres, Moakes, & Norton, 2014; Wu & McClements, 2015).

3.5. Retention and Release Properties

Two of the most important properties of hydrogel beads are their retention and release properties. Typically, a nutraceutical should be retained within the beads until a certain set of environmental conditions is encountered (*e.g.*, the mouth, stomach, small intestine, or colon), and then it should be released. An encapsulated component will be released under circumstances where a hydrogel bead dissociates, *e.g.*, due to erosion or disintegration caused by physical, chemical, or enzymatic means. An encapsulated component may also be released under conditions where the hydrogel beads remain intact. There are two main factors that impact the retention and release of encapsulated substances in this case: pore size and specific interactions. As discussed earlier, a substance (molecule or particle) will be effectively retained within the beads and only released slowly when its dimensions are considerably larger than the pore size of the beads. On the other hand, it will tend to be released when its dimensions are much smaller than the pore size (provided there are no attractive interactions). Consequently, retention and release can be engineered by controlling the pore size of the hydrogel beads, *e.g.*, by using different types or concentrations of biopolymers and cross-linking agents or

by varying environmental conditions such as pH, ionic strength and temperature. The impact of pore size on the release of small curcumin-loaded lipid droplets from calcium alginate beads is shown in **Figure 6** (Zeeb, et al., 2015). When the beads are prepared from low alginate levels they have large pores and rapidly release the lipid droplets, but when they are prepared from high alginate levels they have small pores and therefore only slowly release the lipid droplets.

Alternatively, retention and release can be controlled by engineering the nature of the attractive and repulsive interactions between the nutraceutical and the biopolymer molecules that make up the hydrogel network inside the beads (Lieleg, Baumgartel, & Bausch, 2009). If there is a strong attraction between the nutraceuticals and biopolymers, then the nutraceuticals will tend to be retained well (**Figure 7**). Conversely, if there is no interaction or a repulsion, then the nutraceuticals will tend to be released. Various types of attractive/repulsive interactions can be utilized to control the retention and release of nutraceuticals, with the most commonly used being electrostatic interactions. In particular, the charge on proteins can change from positive at low pH to negative at high pH, while the charge on anionic polysaccharides will decrease when the pH is sufficiently below the pK_a value. This approach has been used to develop pH-triggered release systems for proteins (**Figure 8**) (Zhang, Zhang, Zou, & McClements, 2016c). At pH 3, there is a strong electrostatic attraction between the cationic protein and anionic alginate molecules in the hydrogels, and so the protein is retained. Conversely, at pH 7, there is a strong electrostatic repulsion between the anionic protein and anionic polysaccharide molecules, which causes the protein to be released.

4. Applications

4.1. Protection of Polyunsaturated Fatty Acids

Polyunsaturated fatty acids (PUFAs) are highly susceptible to chemical degradation due to lipid oxidation, which leads to undesirable rancid off-flavors and potentially toxic reaction products (McClements & Decker, 2000). This phenomenon is a major challenge to food manufacturers who would like to incorporate health-promoting ω -3 rich PUFAs into functional foods, such as fish, algal and flaxseed oils (Jacobsen, 2015; Jacobsen, Let,

Nielsen, & Meyer, 2008). Consequently, there has been considerable interest in the potential of hydrogel beads to protect PUFA-rich lipid droplets from lipid oxidation. Studies have shown that lipid droplets trapped within caseinate-pectin hydrogels had better stability to oxidation than non-encapsulated lipid droplets (Matalanis, Decker, & McClements, 2012; Zhang, Decker, & McClements, 2014). This effect was attributed to the fact that caseinate is a highly effective antioxidant, and therefore having a high local concentration of caseinate around the lipid droplets can improve their oxidative stability. A recent study showed that these hydrogel beads could be used as a means of enriching meat products with PUFAs (Salcedo-Sandoval, Cofrades, Ruiz-Capillas, & Jimenez-Colmenero, 2015a; Salcedo-Sandoval, et al., 2015b).

4.2. Protection of Carotenoids

The carotenoids are a group of strongly hydrophobic molecules that have considerable potential as nutraceuticals because of their beneficial health effects, including antioxidant activity, pro-vitamin A activity, and promotion of eye health (Berman, et al., 2015). Numerous carotenoids have been shown to have potentially beneficial biological activities, including β -carotene, lutein, lycopene, zeaxanthin, and astaxanthin. Nevertheless, the utilization of these relatively long non-polar polyunsaturated molecules as nutraceuticals in foods is challenging because of their low water-solubility, chemical instability, and low oral bioavailability. Problems with low water-solubility and bioavailability can often be overcome by dissolving the carotenoids in emulsion- or nanoemulsion-based delivery systems. However, the carotenoids in these systems are still highly susceptible to chemical degradation, especially when stored under acidic conditions or at elevated temperatures (Boon, McClements, Weiss, & Decker, 2009; Qian, Decker, Xiao, & McClements, 2012a, 2012b). Recent studies have shown that the chemical stability of carotenoid-enriched lipid droplets can be improved by trapping them within calcium alginate beads (Zhang, Zhang, & McClements, 2016a).

Hydrogel beads may also be used to modulate the gastrointestinal fate of carotenoids. One recent study showed that carotenoid-enriched lipid droplets had higher bioaccessibility when incorporated into starch-based hydrogels, which was attributed to the ability of the hydrogels to inhibit excessive droplet flocculation in the stomach and small intestine, thereby allowing the lipase to access the lipid droplet surfaces more easily

(Mun, Kim, & McClements, 2015). In another study, carotenoid-enriched lipid droplets were trapped inside hydrogel beads formed by cross-linking starch with sodium trimetaphosphate (Wang, et al., 2015). The carotenoids were retained by the hydrogel beads within the mouth and stomach, but were released once they reached small intestine conditions. This kind of property may be useful for protecting carotenoids from chemical degradation within the highly acid conditions of the stomach, since some carotenoids are known to degrade rapidly at low pH values (Qian, et al., 2012b).

4.3. Protection and Release of curcumin

Curcumin is an important bioactive agent found within the spice turmeric, which has been shown to have a variety of biological activities, such as antioxidant, antimicrobial, anti-inflammatory, and anti-cancer activities (Heger, van Golen, Broekgaarden, & Michel, 2014; Prasad, Gupta, Tyagi, & Aggarwal, 2014). There is therefore considerable interest in incorporating curcumin into a variety of functional foods, supplements, and pharmaceuticals. However, the application of curcumin as a nutraceutical ingredient is often limited because of its low water-solubility and poor chemical stability (Letchford, Liggins, & Burt, 2008). In addition, the potential health benefits of ingested curcumin may be limited because it is rapidly metabolized within the GIT (Anand, Kunnumakkara, Newman, & Aggarwal, 2007; Sharma, Steward, & Gescher, 2007). The low-water solubility of curcumin can be overcome by encapsulating it within lipid droplets in the form of emulsions or nanoemulsions. Nevertheless, the curcumin in these systems is still highly unstable to chemical degradation (Zou, et al., 2015). Recent studies have shown that the chemical stability of curcumin-enriched lipid droplets can be improved by trapping them within polysaccharide-based hydrogel beads (Zhang, et al., 2016b). In this study, calcium alginate or potassium carrageenan beads were fabricated by injecting a mixture of curcumin-loaded lipid droplets and anionic polysaccharides into a gelling solution containing cationic mineral ions. The same study also showed that the release of the curcumin from the beads depended on their composition, which was related to their ability to alter lipid digestion differently. Another recent study showed that curcumin-loaded lipid droplets could also be trapped within calcium alginate beads, and that their release rate depended on the hydrogel pore size, which was controlled by altering the alginate and calcium concentrations (Zeeb, et al., 2015). The rate of lipid droplet release

increased with decreasing calcium level, alginate level, and droplet size.

4.4. Targeted or Triggered Release of Nutraceuticals

Hydrogel beads can be designed so that they remain intact in certain regions of the GIT, but dissociate in other regions of the GIT, and can therefore be designed to release nutraceuticals in response to specific GIT triggers (Zhang, et al., 2015a). Recent studies have shown that hydrogel beads can be designed to breakdown under simulated oral conditions due to a change in pH (Zhang, Zhang, Decker, & McClements, 2015b) or temperature (Zhang, Zhang, Tong, Decker, & McClements, 2015c). The pH-triggered hydrogel beads were fabricated by electrostatic complexation of a protein (caseinate) and an anionic polysaccharide (alginate) at a pH value around or below the isoelectric point of the protein (pH 4 to 5). These beads then dissociated under the neutral conditions of the mouth because both biopolymers became negatively charged. The temperature-triggered hydrogel beads were fabricated using electrostatic complexation of two proteins (caseinate and gelatin). The gelatin molecules undergo a helix-to-coil transition upon heating, which caused the hydrogel beads to dissociate upon heating to around oral temperatures. Calcium alginate beads have been developed to inhibit the digestion and release of lipid droplets in the mouth, stomach, and small intestine, but release them in the colon (Li, et al., 2011a). Another recent study showed that proteins could be retained within calcium alginate beads when the protein and alginate had opposite charges (pH 3), but was released when they had similar charges (pH 7) (**Figure 8**) (Zhang, et al., 2016c).

5. Conclusions

Hydrogel beads have considerable potential for encapsulating, protecting, and releasing nutraceuticals within the food industry. Hydrophilic nutraceuticals can often be simply mixed with a biopolymer solution, and then hydrogel beads can be formed, however, some kind of attractive interaction is required between the nutraceuticals and the biopolymer molecules to ensure that the bioactive agents are retained. Hydrophobic nutraceuticals are usually trapped in lipid droplets first by forming an emulsion or nanoemulsion, and then they are mixed with the biopolymer solution used to form the hydrogel beads. The functional performance of hydrogel beads can be controlled by selecting appropriate biopolymers, cross-linking agents, and preparation methods to

fabricate them. Alterations in bead composition, structure, and charge can lead to changes in their ability to retain, protect, and release nutraceutical agents. Hydrogel beads therefore have considerable potential for overcoming some of the challenges currently limiting the utilization of nutraceuticals in functional foods.

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Figures Captions

“Recent progress in hydrogel delivery systems for improving nutraceutical bioavailability” by D.J. McClements

Figure 1: The formation of nutraceutical-loaded hydrogel beads is typically a two-step process: particle formation and particle gelation. Hydrophobic nutraceuticals would be dissolved within the lipid droplets prior to mixing the biopolymers. In the case of hydrophilic nutraceuticals, they could be directly mixed with the biopolymers prior to particle formation.

Figure 2: Nutraceutical-loaded hydrogel beads can be formed using injection methods. A mixture of nutraceuticals and biopolymers is injected into a gelling solution. Hydrophobic nutraceuticals would be dissolved within the lipid droplets prior to mixing with the biopolymers. Hydrophilic nutraceuticals would be directly mixed with the biopolymers.

Figure 3: Nutraceutical-loaded hydrogel beads can be formed using emulsion templating methods. An aqueous solution containing a mixture of nutraceuticals and biopolymers is homogenized with an oil phase to form a water-in-oil emulsion, and then the inner water phase is gelled by cross-linking the biopolymers. The outer oil phase can then be removed by centrifugation, filtration and/or solvent extraction. Hydrophobic nutraceuticals would be dissolved within the lipid droplets prior to mixing with the biopolymers. Hydrophilic nutraceuticals would be directly mixed with the biopolymers.

Figure 4: Nutraceuticals (molecules or particles) may be released from hydrogel beads through a number of different mechanisms.

Figure 5: Nutraceuticals (molecules or particles) will be retained if their dimensions are appreciably greater than the pore size of the hydrogel beads.

Figure 6: The release of curcumin-loaded lipid droplets from calcium alginate beads (after 24 hour storage) decreased with increasing alginate concentration, which was attributed to a decrease in pore size (Zeeb et al 2015).

Figure 7: Nutraceuticals (molecules or particles) will be retained if there is a strong enough attraction to the biopolymer molecules in the hydrogel beads.

Figure 8: The impact of preparation pH on the retention of protein in calcium alginate beads (Zhang et al 2016). The amount of protein encapsulated decreased with increasing pH due to weakening of electrostatic attraction between the protein molecules and alginate in the hydrogel matrix (Zhang et al 2016).

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Simple Diffusion

Swelling & Diffusion

Disintegration & Diffusion

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