Comprehensive REVIEWS in Food Science and Food Safety

Delivery by Design (DbD): A Standardized Approach to the Development of Efficacious Nanoparticle- and Microparticle-Based Delivery Systems

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Abstract: The design and development of nanoparticle- and microparticle-based delivery systems for the encapsulation, protection, and controlled release of active agents has grown considerably in the agrochemical, cosmetic, food, personal care, and pharmaceutical industries. These colloidal delivery systems can be utilized to overcome problems such as poor solubility, low activity, and chemical instability of active agents, as well as to create novel functional attributes such as controlled or targeted delivery. The purpose of this article is to develop a systematic approach, referred to as "delivery-by-design" (DbD), to make the design and fabrication process more efficient and effective. Initially, a brief review of some of the challenges associated with incorporating active agents into commercial products is given, and then an overview of different kinds of simple and complex colloidal delivery systems is given. The DbD approach is then presented as a series of stages: (1) definition of the molecular and physicochemical properties of the active agent; (2) definition of the required physicochemical, sensory, and functional attributes of the end-product; (3) specification of the required attributes of the colloidal delivery system; (4) specification of particle properties and delivery system selection; (5) optimization of delivery system manufacturing process; (6) establishment and implementation of delivery system testing protocol; and (7) optimization of delivery system performance. Utilization of the DbD approach may lead to more rapid design of efficacious and economically viable colloidal delivery systems for commercial applications.

Keywords: delivery systems, encapsulation, microparticles, nanoparticles, rational design

Introduction

There has been a surge of interest in the development of colloidal delivery systems over the past decade or so, with numerous research and review articles being published in this area (Oh and others 2008; Kumari and others 2010; Petros and DeSimone 2010). Indeed, there has been over 60000 articles published on the use of nanoparticles or microparticles as delivery systems within the past 10 y (Web of Science, Thomson Scientific). These colloidal delivery systems are primarily being designed to encapsulate, protect, and release active agents in the pharmaceutical, food, cosmetic, agrochemical, and other industries. The encapsulated active agents include drugs, vitamins, nutraceuticals, nutrients, antimicrobials, antioxidants, flavors, and colors. The main reason for developing these delivery systems is to overcome challenges that normally limit the incorporation of these active agents into commercial products, such as poor solubility characteristics, susceptibility to chemical degradation, undesirable flavor profiles, low bioavailability, or limited bioactivity (McClements 2014). Numerous kinds of colloidal delivery system have been developed for this purpose, including microemulsions, nanoemulsions, emulsions, solid lipid nanoparticles, liposomes, biopolymer nanoparticles, and microgels (Oh and others 2008; McClements 2014; Aditya and others 2017). Recently, there has been considerable interest in extending the functional attributes of conventional colloidal delivery systems by utilizing structural design approaches, such as coating, embedding, clustering, or mixing techniques (McClements 2012b; Joye and others 2014). The research carried out so far clearly shows that colloidal delivery systems have considerable potential for many applications in medicine and industry. Nevertheless, many of the research articles published in this area do not have a clear appreciation of the practical challenges that delivery systems must overcome before they are suitable for commercial applications. Indeed, many of the colloidal delivery systems that have been developed would not be commercially viable because they are too expensive, too difficult to manufacture, contain constituents unacceptable for the intended application, or do not function under the environmental conditions that they would encounter in commercial practice.

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doi: 10.1111/1541-4337.12313

Table 1–Terminology related to colloidal delivery system design.

Term	Meaning
Active agent	An active agent can be any substance that needs to be encapsulated and delivered, such as an antimicrobial, antioxidant, flavor, color, nutraceutical, nutrient, pharmaceutical, and so on.
Carrier materials	Carrier materials are any substances that can be utilized to create the colloidal particles used to encapsulate the active agent, and include surfactants, lipids, polymers, water, minerals, antioxidants, chelating agents, buffers, and so on.
Nanoparticle	A colloidal particle with a mean diameter within the range from 1 to 100 nm.
Microparticle	A colloidal particle with a mean diameter in the range from 100 nm to 1000 μm.
Colloidal delivery system	A delivery system comprised of either nanoparticles and/or microparticles.
End product	The end product is the commercial product that the delivery system will be incorporated into, and may be a food, beverage, drug, cosmetic, shampoo, and so on.

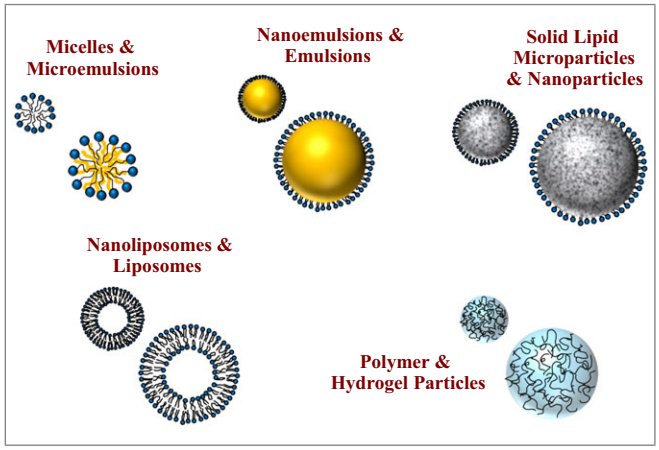

Figure 1–Examples of simple colloidal delivery systems that can be used to encapsulate, protect, and deliver active agents (not drawn to scale).

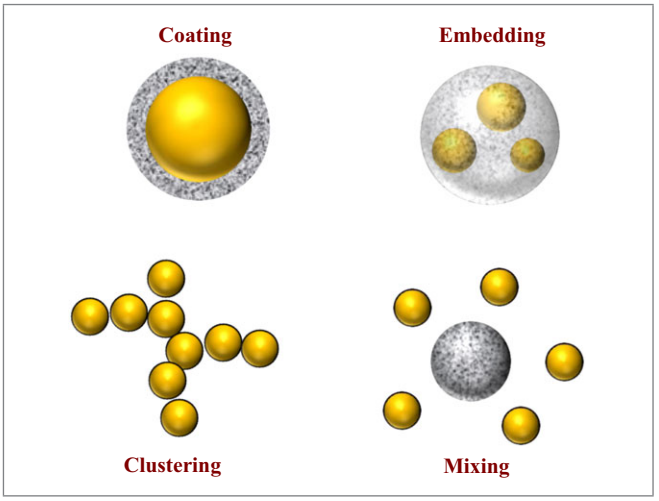

Figure 2–General approaches for creating more complex structured colloidal delivery systems: coating; embedding; clustering; mixing.

The purpose of this article is to present a systematic approach, called "delivery by design" (DbD), for developing colloidal delivery systems for specific applications. This approach could be used by academic and industrial researchers to identify the most suitable colloidal delivery system for a particular application, and to optimize its fabrication and performance. The DbD approach is related to the "Quality by Design" (QbD) approach that has been developed to ensure the efficacy and safety of pharmaceutical products (Singh and others 2011; Rantanen and Khinast 2015; Bastogne 2017). However, the DbD approach is more focused on selecting and optimizing the functional performance of colloidal delivery systems suitable for a broad range of pharmaceutical and nonpharmaceutical applications. Some of the terminology used throughout this manuscript when referring to active agents and delivery systems is summarized in Table 1. The main focus of this article will be on colloidal delivery systems containing organic particles, such as those fabricated from proteins, carbohydrates, lipids or surfactants, rather than those fabricated from inorganic particles.

Overview of Colloidal Delivery Systems

Numerous kinds of simple and complex colloidal delivery systems have been investigated for their potential to encapsulate, protect, and deliver active agents (Figure 1 and 2). The common theme of all of these systems is the fact that they contain small particles, which can be referred to as nanoparticles ($1 < d < 100$ nm) or microparticles (100 nm $< d <$ 1000 μm) depending on their dimensions (McClements 2014). These particles may vary considerably in their compositions, sizes, shapes, structures, and charges, which leads to differences in their functional attributes, such as their impact on the optical properties, rheology, stability, and release characteristics of a delivery system. In this section, a brief overview of the most commonly used colloidal delivery systems is given. More detailed information about each of these delivery systems can be found in the literature cited. For convenience, these systems are characterized as either simple or complex depending on their structural complexity. Complex delivery systems are usually prepared by utilizing simple delivery systems as building blocks using structural design principles, such as embedding, coating, clustering, or mixing (Figure 2). In this discussion, we will restrict ourselves to systems that consist of colloidal particles dispersed in water, since these are the most commonly used for encapsulation and delivery purposes.

Simple delivery systems

Simple delivery systems are usually fabricated using a simple key processing operation, such as mixing, homogenization, or injection. In this section, the most widely used simple colloidal delivery systems are briefly discussed.

Micelles and microemulsions. Micelles consist of small clusters of surfactant molecules that self-assemble into a structure where the hydrophobic tails are located in the interior, whereas the hydrophilic heads are located at the exterior (Figure 1) (Flanagan and Singh 2006; Narang and others 2007; Gupta 2011; Garti and Aserin 2012). Micelles are thermodynamically stable systems under a particular range of compositional and environmental conditions, and should therefore form spontaneously. Nevertheless, some form of energy often has to be applied during their formation (such as simple mixing) to overcome kinetic energy barriers to the self-assembly of the surfactant molecules (McClements 2012a). Micelles are one of the smallest colloidal particles that are widely used as delivery systems, with diameters typically in the range from about 5 to 20 nm. Nonpolar active agents

can be solubilized within the hydrophobic interior of micelles, whereas amphiphilic active agents can be incorporated at their exterior, with the loading capacity depending on the molecular dimensions of the active agents and the optimum curvature of the surfactant monolayer. Microemulsions have very similar structures as micelles, but they may also contain an oil phase and possibly a co-surfactant. Consequently, they tend to have larger dimensions (typically $10 < d < 100$ nm) than microemulsions, and can solubilize higher levels of nonpolar active agents. These types of delivery systems are usually fabricated from small molecule surfactants, but amphiphilic block copolymers can also be used.

Emulsions and nanoemulsions. In some respects, emulsions and nanoemulsions have similar structures to microemulsions, consisting of an oily core covered by a layer of surfactant molecules (Figure 1). However, these systems are thermodynamically unstable and will, therefore, not form spontaneously (Tadros and others 2004; Solans and others 2005; Gutierrez and others 2008; McClements 2011; McClements and Rao 2011). Instead, they have to be formed using high- or low-energy methods that rely on the utilization of mechanical or chemical energy for their formation. By definition, nanoemulsions contain smaller droplets (typically $10 < d < 100$ nm) than emulsions (typically 100 nm $< d <$ 100 μm), which can lead to appreciable differences in their physicochemical properties and functional attributes. For example, the smaller size of the droplets in nanoemulsions often leads to better stability to droplet aggregation and gravitational separation, higher optical clarity, and greater bioavailability of encapsulated active agents.

Solid lipid nanoparticles and nanostructured lipid carriers. Solid lipid nanoparticles (SLNs) have similar structures to nanoemulsions (or emulsions), but the oil phase is crystallized rather than liquid (Figure 1) (Muller and others 2000; Wissing and others 2004; Kesisoglou and others 2007; Pardeike and others 2009). Typically, the term SLN is used to refer to any colloidal system that contains relatively small crystalline lipid particles. However, to be more precise, it would be better to define SLNs as having diameters <100 nm and solid lipid microparticles (SLMs) as having diameters >100 nm. However, the traditional terminology (SLN) will be utilized here to refer to both types. SLNs are typically fabricated by preparing an oil-in-water nanoemulsion at a temperature above the melting point (T_m) of the oil phase, and then cooling the system well below T_m to promote droplet crystallization. In principle, the crystallization of the lipid phase slows down molecular diffusion processes inside the particles, which may help to protect an encapsulated active agent from chemical degradation. SLNs have proven to be useful delivery systems for many applications in the pharmaceutical industry, where they are mainly used to encapsulate hydrophobic drugs. However, if the lipid phase is not carefully selected there can be appreciable challenges to their utilization for this purpose. Lipids that form highly regular crystalline structures (such as pure triacylglycerols) have a tendency to expel other nonpolar substances when they undergo a liquid-to-solid transition. Moreover, there may be an appreciable change in the morphology of the lipid nanoparticles, from spherical to irregular, when the lipid phase crystallizes or undergoes a polymorphic transition. As a result of the increase in particle surface area, there may be insufficient emulsifier to coat the particles, which leads to extensive aggregation (Helgason and others 2009). These problems can be overcome by using nanostructured lipid carriers (NLCs). In this case, a lipid phase is selected that forms more irregular crystals when it solidifies, which leads to less expulsion of encapsulated active agents and less particle aggregation.

Liposomes and nanoliposomes. Liposomes ($d >$ 100 nm) and nanoliposomes ($d <$ 100 nm) are colloidal systems that are comprised of particles made up of concentric layers of phospholipid bilayers (Figure 1) (Taylor and others 2005; Mozafari and others 2008; Malam and others 2009; Sawant and Torchilin 2010; Maherani and others 2011; Deshpande and others 2013). The bilayers form due to the hydrophobic effect, that is, the tendency for the system to reduce the contact area between the nonpolar phospholipid tails and water. These systems may contain 1 (unilamellar) or numerous (multilamellar) phospholipid bilayers depending on the preparation method and ingredients used. Hydrophilic functional ingredients can be trapped inside the aqueous interior of liposomes and nanoliposomes, whereas amphiphilic and lipophilic active agents can be trapped in the bilayer region. There is considerable interest in utilizing liposomes as delivery systems because they can be fabricated from natural components, such as phospholipids. However, it is often difficult to achieve high loading and retention of active agents within liposomes, and their structure is often quite fragile, and so it is challenging to create delivery systems that will remain stable under the harsh conditions in many commercial end-products.

Polymer and hydrogel particles. Polymer microparticles ($d >$ 100 nm) and nanoparticles ($d <$ 100 nm) are fabricated from either synthetic or natural polymers (such as proteins and polysaccharides) (Figure 1) (Oh and others 2008; Joye and McClements 2014). Commonly, they are produced from antisolvent precipitation methods where a polymer dissolved in a good solvent is injected into a poor solvent, which promotes spontaneous particle formation. Hydrogel particles (sometimes called nanogels or microgels) may also be fabricated from synthetic or natural polymers, but they contain higher levels of water (typically >80% to 90%). A wide variety of different methods are available for producing hydrogel particles including injection, templating, emulsion, and phase separation methods (McClements 2017). The composition and porosity of hydrogel particles must be carefully controlled to ensure appropriate loading, retention, and release properties (Figure 3a and 4b).

Complex delivery systems

Complex delivery systems are usually fabricated by applying structural design principles to modify the properties and functionality of simple delivery systems (Figure 2) (McClements 2017). In this section, some of the major structural design principles that are typically used are highlighted.

Coating. The functional attributes of colloidal particles can often be enhanced or extended by coating them with other materials. For instance, coating can be used to alter their electrical properties, stability, interactions, retention, and release characteristics (McClements 2014). One of the most common approaches used to coat colloidal particles is the layer-by-layer (LbL) electrostatic deposition method (Johnston and others 2006; Wang and others 2008; Tong and others 2012). In this approach, an electrically charged particle is coated by a layer of another oppositely charged substance, such as an ionic polymer or particle. This approach can be repeated many times to form multiple layers around a colloidal particle. The LbL approach has previously been used to coat lipid droplets (Guzey and McClements 2006), SLNs (Finke and others 2013), liposomes (Laye and others 2008; Chun and others 2013), and microgels (Zhao and others 2014). Other coating approaches include complex coacervation and Pickering stabilization. In complex coacervation, colloidal particles are coated by a relatively thick layer of a coacervate phase, which is usually

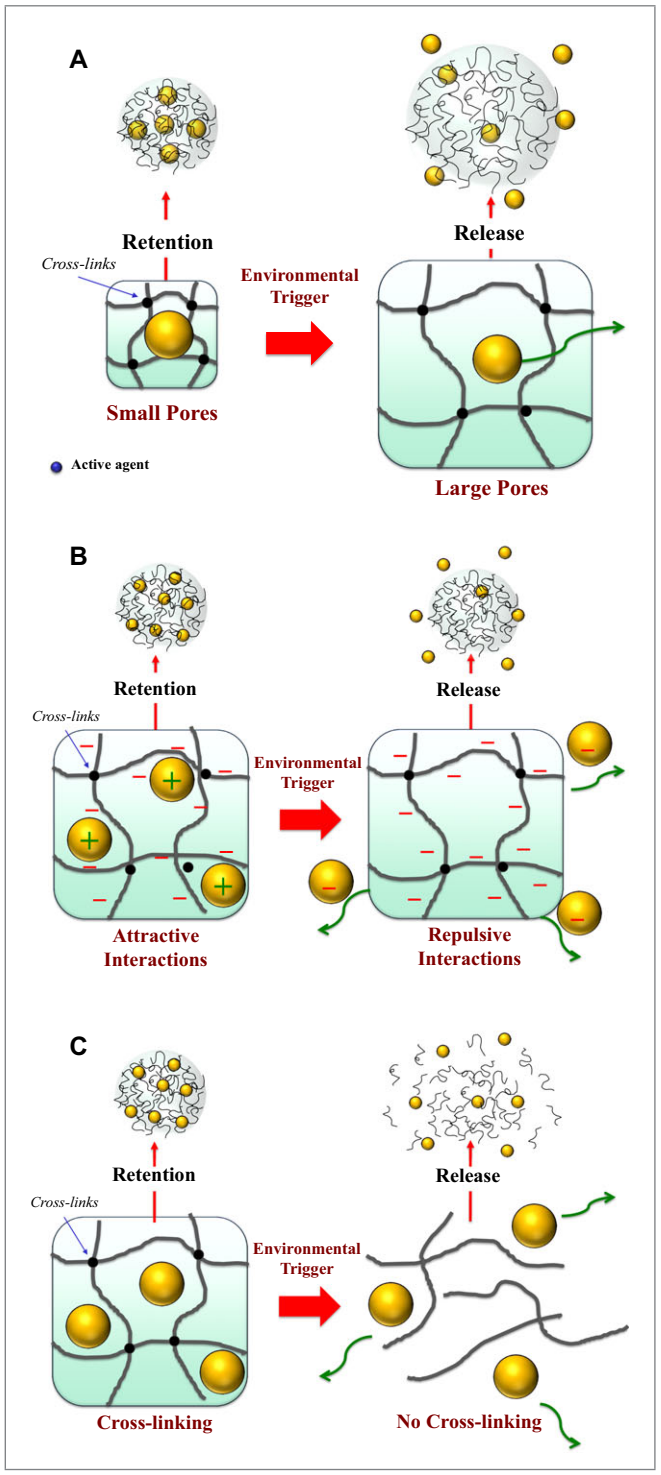

Figure 3–The release of active components (yellow spheres) can be controlled by varying the pore size or interactions of the biopolymer matrix within the microgel interior.

comprised of protein and polysaccharide molecules held together by electrostatic attraction (Devi and others 2017). In the Pickering method, larger colloidal particles are coated by a layer of smaller colloidal particles that are able to adsorb to their surfaces (Xiao and others 2016). This approach is commonly used to stabilize large oil droplets by adsorbing small organic or inorganic nanoparticles to their surfaces (Dickinson 2017).

Embedding. The functionality of colloidal particles can also be modulated by encapsulating them within larger structures (Zhang and others 2015; van Leusden and others 2016). Multiple emulsions are a common example of colloidal delivery systems that are produced using this approach (Khan and others 2006; Muschiolik 2007). For example, water-in-oil-in-water ($W_1/O/W_2$) emulsions consist of small water droplets embedded within larger oil droplets that are themselves dispersed in water. There are a number of potential advantages to developing this kind of more complex emulsion-based delivery system. First, it is possible to encapsulate hydrophilic, lipophilic, and amphiphilic active agents within the same system. Second, hydrophilic active agents that normally have poor taste profiles (such as bitter peptides or drugs) can be encapsulated within the interior water phase (W_1) so that they are not perceived in the mouth, but are still released in the stomach or small intestine. Third, 2 different hydrophilic agents that normally react with each other can be separated by dispersing one in the internal water phase (W_1) and the other in the external water phase (W_2). Finally, multiple emulsions can be used to control the release rate of encapsulated substances by trapping the active agent in the interior water phase so that it is only released once the oil phase has broken down.

The embedding approach can also be used to modify the properties of other types of colloidal dispersion so as to enhance their functional attributes. For example, nanoparticles can be embedded in microparticles to improve their stability or to control their release profile (McClements 2017). As an example, lipid droplets have been trapped inside calcium alginate microgels so as to protect them from degradation during storage, but then to release them in response to a specific environmental trigger (Zeeb and others 2015a, 2015b). In general, nanoparticles can be released from microgels by changing temperature, pH, ionic strength, or enzyme activity to alter the pore size (Figure 3a), interactions (Figure 3b), or integrity (Figure 3c) of the polymer network. For instance, protein-coated lipid droplets have charges that change from negative to positive when the pH is decreased from above to below the protein's isoelectric point (pI). Consequently, they are attracted to anionic alginate molecules inside the microgels at low pH (retained), but repelled at high pH (released). This approach has also been employed to protect lipid droplets from digestion in the upper GIT, and then release them in the colon (Li and others 2011). Microgels may also be used to control the digestion rate of lipid droplets within the small intestine, as well as the bioaccessibility of encapsulated hydrophobic bioactives (such as curcumin) (Zhang and others 2016a).

Mixed colloidal delivery systems. Typically, the colloidal delivery systems used to encapsulate active agents contain a single kind of particle, such as lipid droplets, solid lipid nanoparticles, liposomes, or polymer particles (Patel and Velikov 2011; McClements 2014; Livney 2015). Nevertheless, for certain applications it may be an advantage to use colloidal delivery systems containing a mixture of 2 or more different kinds of colloidal particles, such as lipid droplets and polymer particles. As an example, it was recently shown that delivery systems consisting of a mixture of lipid nanoparticles and curcumin-loaded protein nanoparticles were more effective than those containing only a single type of curcumin-loaded nanoparticle (Chen and others 2015; Zou and others 2016). The protein nanoparticles protected the curcumin from chemical degradation and had a high loading capacity, whereas the lipid nanoparticles provided a source of digestible triglycerides that increased the solubility of the curcumin in the gastrointestinal fluids by forming mixed micelles. This principle

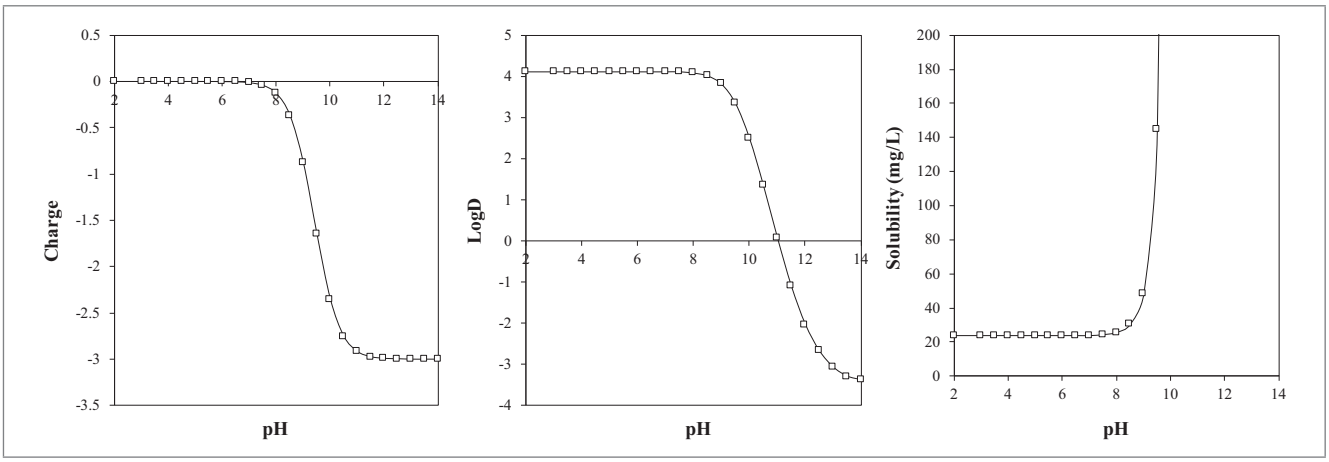

Figure 4—The properties of bioactive agents often depend on pH due to the presence of ionizable groups, which alters physical interactions and chemical reactions. In this example, the impact of pH on the electrical charge, partition coefficient, and solubility of curcumin is shown (data from chemicalize.com).

can also be utilized to form mixed colloidal delivery systems with novel or extended functionalities. For example, by encapsulating lipid droplets in a mixture of both small and large microgels it is possible to control the lipid digestion profile under simulated GIT conditions: the lipid droplets in the smaller microgels are digested and released more rapidly than those in the larger microgels (Zhang and others 2016b).

Clustering. The functional properties of colloidal delivery systems can also be modulated by altering the aggregation state of the particles (Mao and McClements 2013a). Often, colloidal delivery systems are carefully designed to avoid particle aggregation by ensuring that there is a strong repulsion between the particles. However, novel functional attributes can be obtained by creating delivery systems that contain clusters of colloidal particles (Golding and Wooster 2010; Mao and McClements 2012). For example, the rate of lipid digestion may be retarded when the lipid droplets in a nanoemulsion are highly aggregated, because this restricts the access of lipase to the droplet surfaces (Golding and Wooster 2010; Golding and others 2011; Mao and McClements 2012). Clustering can be induced by increasing the attractive interactions (such as van der Waals or hydrophobic) or reducing the repulsive interactions (such as electrostatic or steric) between similar types of colloidal particles (McClements 2015). Alternatively, clustering can be induced by mixing cationic and anionic colloidal particles together (Mao and McClements 2013a, 2013b; Maier and others 2014) or by mixing charged colloidal particles with oppositely charged polymers (Simo and others 2012). The size, shape, porosity, and strength of the clusters formed can be modulated by altering the strength of the colloidal interactions. In general, various types of oppositely charged colloidal particles can be utilized to create clusters, including polymer particles, lipid droplets, SLNs, or microgels.

Delivery by Design

A systematic multistage approach for designing colloidal delivery systems for specific applications is presented in this section.

Stage 1: Active agent definition

The first step in the successful design of a colloidal delivery system is to carefully analyze the molecular and physicochemical properties of the active agent, and to specify its desired functional attributes. These attributes are highly dependent on the specific application, and so it is difficult to give general guidelines for all applications. For example, the active agent may have to perform as a drug, nutraceutical, flavor, color, antioxidant, or antimicrobial with specific functional requirements, such as controlled or triggered release. Nevertheless, a number of important factors can be highlighted, which will be appropriate for many active agents, such as their solubility, chemical reactivity, and charge characteristics. Many of the most important properties of active agents can be found in the literature, either from experimental measurements or from predictive models. If the data cannot be found, then it may be necessary to carry out experiments to obtain them.

Molecular and physicochemical characteristics. It is useful to characterize the molecular and physicochemical properties of the active agent so as to better understand its behavior in the final application. This information provides valuable insights into the type of delivery system that may be most appropriate. Some of the most important molecular and physicochemical properties are highlighted below:

- *Chemical formula and structure*: Knowledge of the chemical formula and structure of an active agent provides valuable insights into its polarity, charge distribution, and chemical reactivity.
- *Molar mass*: The molar mass of a molecule is important for calculating its concentration within a delivery system, as well as determining other important properties.
- *Molecular dimensions*: Information about the size of a molecule may be useful for determining its ability to pass through small pores in delivery systems (such as those in microgels or interfacial layers), which will impact its retention and release. Moreover, knowledge of the molecular dimensions may be important when developing appropriate separation or analytical methods, such as filtration, dialysis, or chromatography. Most molecules are not spherical, but to a first approximation their effective radius can be calculated from the molecular volume (V) using the relationship: $r = (3V/4\pi)^{1/3}$.
- *Density*: The density (ρ) of a pure substance influences the rate of gravitational separation in a colloidal delivery system. If the active agent is diluted in a solvent, then the overall density of the mixture is more important.
- *Refractive index*: The refractive index (n) of a pure substance influences its ability to reflect or scatter light, which impacts the optical properties (appearance) of colloidal delivery

systems. If the substance is diluted in a solvent, then the overall refractive index of the mixture is more important.

- *Melting and boiling points*: The temperature at which a substance undergoes phase transitions, such as melting-crystallization, glass-rubbery, boiling-condensation, or helix-coil is often important in the design and fabrication of delivery systems. For example, it may be necessary to melt or dissolve a crystalline active agent before it can be successfully incorporated into a delivery system.
- *Partitioning*: The logarithm of the oil-water partition coefficient (*LogP*) determines the distribution of a substance between the polar and nonpolar regions within a heterogeneous material (such as an emulsion, nanoemulsion, or liposome suspension). This parameter is extremely important for many applications as it determines the preferred location of an active agent within a colloidal delivery system (oil, water, or interfacial phase), which impacts the loading, retention, and release characteristics. Moreover, the molecular environment of a substance can influence its chemical stability, with some substances being much more stable in an oil phase than an aqueous phase.
- *Diffusion coefficient*: The rate at which a substance diffuses through the oil, water, and interfacial phases in a colloidal dispersion determines the retention and release characteristics. Sometimes it is possible to find published values for the translational diffusion coefficients (D) of substances in different solvents. In cases where they cannot be found, it is possible to estimate the value using the following equation: $D = kT/(6\pi\eta r)$, where k is Boltzmann's constant, T is the absolute temperature, η is the shear viscosity of the surrounding solvent, and r is the effective radius of the molecule (assuming it is approximately spherical).
- *Molar volume*: The molar or molecular volume of a substance provides a useful estimate of its molecular dimensions.
- *Surface tension*: The surface tension of a pure active agent provides a measure of its polarity: the lower the surface tension, the less polar it is.
- *Solubility*: The solubility characteristics play a critical role in the design of colloidal delivery systems and are therefore discussed in more detail below.
- *pK_a values*: The pH values where the chemical groups on a substance change their ionization state plays a critical role in determining the functional attributes of many colloidal delivery systems. A change in the electrical characteristics of an active agent may change its chemical reactivity and physical interactions, as well as its solubility and partitioning behavior (Figure 4). Consequently, it is important to determine if a substance has any pK_a values within the range of conditions that it may experience during manufacture, storage, and utilization. Moreover, it is important to determine the nature of the change in the ionization state, for example, from neutral to negative.
- *Hydrogen bond acceptors/donors*: If a substance has hydrogen bond acceptors or donors, then its chemical reactivity and charge may change with pH.

As an example, a number of the most important molecular and physicochemical properties of an important nutraceutical (curcumin) are shown in Table 2. Most of these values were obtained from on-line chemical databases (such as chemspider.com and chemicalize.com). The impact of pH on the properties of curcumin is highlighted in Figure 4. The curcumin becomes increasingly negatively charged at high pH values due to deprotonation of hydroxyl groups. As a result, it becomes more polar, water-soluble, and chemically unstable.

Table 2–Summary of selected molecular and physicochemical properties of curcumin taken from on-line databases (chemspider.com and chemicalize.com). The values marked with an * are highly dependent on pH. In particular, the solubility of curcumin tends to increase as the pH increases above about 7 due to a change in its charge (Figure 4).

Property	Value
Molecular formula	$C_{21}H_{20}O_6$
Molar mass (Da)	368.380
Density	1300
Refractive index	1.643
Melting point (°C)	180
Boiling point (°C)	521.3
LogP*	4.12
Molar volume (cm^3)	287.9
Van der Waals volume (A^3)	330
Estimated effective radius (nm)	4.3
Surface tension (dyne/cm)	54.3
Water solubility (mg/L)*	24
pK_a values	8.1, 9.5, 10.1
Hydrogen bond acceptors	6
Hydrogen bond donors	2

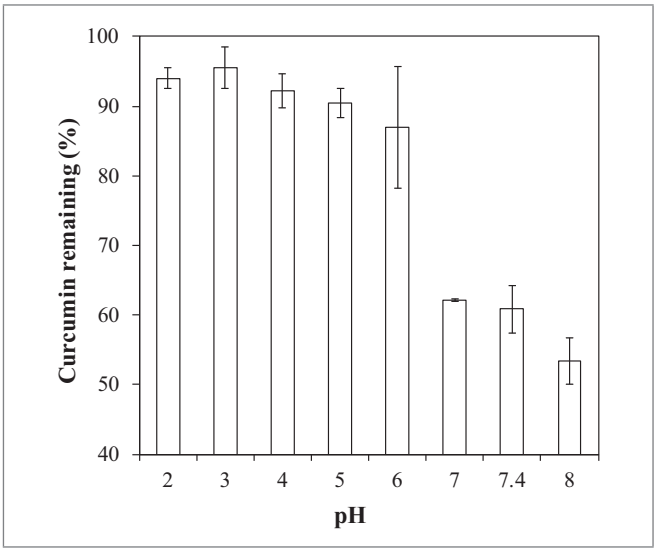

Figure 5–The rate of chemical degradation of many bioactive agents depends on pH. In this example, the impact of pH on degradation of curcumin is shown after 1 mo storage at 37 °C (Kharat and McClements 2017).

Solubility characteristics. The solubility of an active agent is the total amount that can be dissolved in a particular solvent at a particular temperature when equilibrium has been reached (Jorgensen and Duffy 2002; Lipinski and others 2012). The solubility characteristics of an active agent are important for a number of reasons: (1) they determine the phase that is most appropriate for carrying the substance (usually oil or water); (2) they determine the maximum amount of the active agent that can be incorporated into a delivery system; (3) they influence the retention and redistribution of the active agent in the system; and (4) they influence the rate of Ostwald ripening, which is the growth of large particles and the shrinkage of small particles due to diffusion of a substance through the intervening medium. The solubility characteristics of an active agent are mainly determined by its molecular weight, oil-water partition coefficient, and number of hydrogen

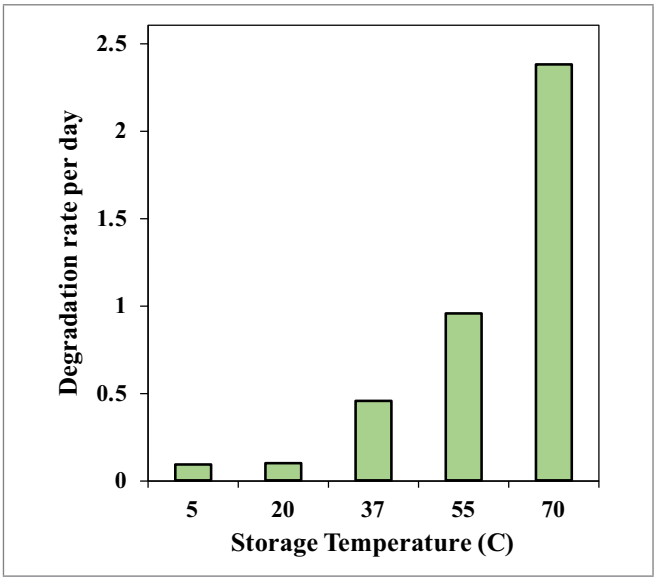

Figure 6–The rate of chemical degradation of many bioactive agents depends on temperature. In this example, the impact of storage temperature on the initial degradation rate (color fading) of lutein in oil-in-water nanoemulsions is shown (Gumus, Davidov Pardo, and McClements 2016).

donors/receptors (Lipinski and others 2012). It should be noted that the solubility characteristics of an active agent may change appreciably when environmental conditions are altered, such as pH, ionic strength, temperature, or matrix composition. For instance, the solubility of curcumin increases appreciably when the pH increases above about 8 because the molecule gains some negative charge, and therefore becomes more polar (Figure 4).

Stability characteristics. Many substances are susceptible to chemical or biochemical transformations when they are exposed to specific solution or environmental conditions. These changes may either be reversible or irreversible depending on the system. It is therefore important to establish the range of conditions where the active agent is stable and the range where it is unstable, and to determine the major factors that have an impact on the degradation rate. The factors that determine degradation depend on the specific chemical groups on the active agent, and they will therefore vary considerably from system to system. Some of the major factors to be considered are given below:

- *pH*: The degradation of many substances depends on the pH of the surrounding solvent, that is, the concentration of H^+ or OH^- ions present. For example, curcumin is known to degrade rapidly under alkaline conditions (Figure 5), which is partly so because some of the hydroxyl groups become deprotonated under these conditions, which increases their chemical reactivity (Heger and others 2014). Conversely, β-carotene degrades rapidly under acidic conditions due to the formation of ion pairs that dissociate (Boon and others 2010). For pH-sensitive active agents, it is important to ensure that they do not experience pH conditions that promote degradation during manufacture, storage, and utilization.
- *Temperature*: The degradation rate of most active agents increases as the temperature increases (Peleg and others 2012). However, the critical temperature where the degradation rate rises steeply depends on the active agent involved and the environmental conditions (such as pH, ingredient interactions, and solvent type). Changes in temperature may also cause physical changes in an active agent, such as conformation changes (such as helix-coil transitions) or phase changes (such as melting and crystallization), which may impact its degradation. An example of the increase in degradation rate of lutein encapsulated in oil-in-water nanoemulsions with increasing temperature is shown in Figure 6. For temperature-sensitive active agents, it is important to ensure that they are not exposed to elevated temperatures that may promote their rapid degradation.
- *Oxygen levels*: The degradation rate of active agents that are susceptible to oxidation (such as polyunsaturated lipids) typically increases as the concentration of dissolved oxygen in their surroundings increases (Johnson and others 2017). For these systems, it is often important to reduce the level of oxygen in the system by pulling a vacuum, flushing with nitrogen, or using chemical reagents, although it is often difficult to maintain the low levels required to inhibit oxidation.
- *Pro-oxidant levels*: The degradation rate of active agents prone to oxidation may also be accelerated by the presence of pro-oxidants in a system, such as transition metals, hydroperoxides, and oxidizing enzymes (McClements and Decker 2000; Waraho and others 2011). These pro-oxidants may only have to be present at very low levels to promote oxidation, and may arise from the water, ingredients, containers, or equipment used to fabricate colloidal delivery systems. In this case, it may be important to remove or deactivate these pro-oxidants, or to ensure that they do not get into the delivery system in the first place.
- *Light exposure*: Certain active agents have functional groups that are susceptible to chemical degradation when exposed to specific wavelengths of UV-visible light (Glass and others 2004; Yan and Song 2014). Typically, the degradation rate of these substances increases as the light intensity increases. Photosensitive active agents may therefore have to be stored under conditions where they are not exposed to light.

In summary, it is important to identify the most important factors that determine the chemical degradation of the active agent to be encapsulated, and then to establish how the degradation rate depends on these factors. Colloidal delivery systems and other strategies may then be developed to overcome these challenges.

Stage 2: End-product definition

Once the properties of the active agent to be delivered have been carefully defined, then it is important to define the properties of the end-product that it is going to be incorporated into. In the pharmaceutical or supplements industries, this may be a capsule, pill, tablet, or fluid. In the cosmetics and personal care industries, this may be a lotion, cream, shampoo, lipstick, toothpaste, or powder. In the food industry, this may be a hot beverage, soft drink, cream, yogurt, sauce, dressing, breakfast cereal, snack bar, cookie, bread, and so on. Each of these commercial products has its own unique requirements, and so again it is difficult to give general recommendations that are applicable to every product. Nevertheless, some important factors that are common to many different products can be identified.

Compositional analysis. The nature of the various constituents within an end-product may impact the properties of both the active agent and the colloidal delivery system. It is therefore important to identify any constituents in the end-product that could alter the performance of the delivery system. These constituents could physically or chemically interact with the active agent or delivery

system, thereby improving or reducing their stability and performance. Some of the most important compositional attributes are pH, ionic strength, and polymer type:

- *pH*: The physical and chemical stabilities of many active agents and colloidal delivery systems are highly sensitive to pH, and therefore it is important to specify the expected pH range of the final product, as well as any pH changes that might occur during and after manufacture.
- *Ionic strength*: Many colloidal delivery systems are stabilized against aggregation because the particles have an electrical charge and so there is a strong electrostatic repulsion between them (Israelachvili 2011). Electrostatically stabilized systems may become unstable when the salt concentration is increased due to electrostatic screening and ion-binding effects. The magnitude of these effects depends on the type and level of counter-ions present in the system, with multivalent ions being more effective than monovalent ions. Consequently, it is important to specify the range of ionic compositions within an end-product during and after fabrication. This may depend on the type and level of ingredients added, as well as the quality of the water used to prepare the product.
- *Transition metals*: Transition metals, such as iron and copper, are highly effective at accelerating the oxidation of unsaturated active agents (Waraho and others 2011). Consequently, it may be important to establish the levels of these pro-oxidants expected in the end-product.
- *Polymers*: Many commercial products contain ionic or non-ionic polymers that may interfere with the stability and performance of colloidal delivery systems (McClements 2015). Polymers may promote particle aggregation through depletion or bridging mechanisms when they are present in sufficient quantities. The interaction between the particles in the colloidal delivery system and any polymers in the final product depends on their molecular characteristics, such as molar mass, conformation, rigidity, hydrophobicity, and charge. Consequently, it may be necessary to characterize the nature of the polymers present in the final product.
- *Surface-active substances*: Surface-active substances in end-products may adsorb to the surfaces of colloidal particles and alter their interfacial characteristics, such as surfactants, phospholipids, and proteins (McClements 2015). As a result, they may change the functional attributes of the delivery system in an undesirable or unexpected way. Consequently, it may be important to establish the types and levels of surface-active substances that are likely to be present within the end-product, and determine how they are likely to interact with the colloidal particles.

A detailed analysis of the composition of the end-product may therefore be required to ensure that the colloidal delivery system will successfully operate under these conditions. Indeed, it is useful to tabulate the type and concentration of the major constituents in an end-product, and especially those that would be expected to interact with the active agent or delivery system.

Environmental stress analysis. A commercial product may be subjected to a variety of environmental stresses during its manufacture, storage, and utilization, including exposure to different temperatures, oxygen levels, and light conditions:

- *Temperature*: The physical and chemical stability of many active agents and colloidal delivery systems strongly depends on temperature. The range of temperatures that an end-product is exposed to should therefore be clearly defined, which might involve freezing, chilling, or thermal processing (such as pasteurization, sterilization, warming, or cooking).
- *Oxygen*: If an active agent to be encapsulated is sensitive to oxidation, then the oxygen level in the commercial product will be important, and it may have to be monitored and controlled. It may therefore be important to define the oxygen levels in the product throughout its manufacture, storage, and utilization.
- *Light exposure levels*: If an active agent is photosensitive, then the light levels in the commercial product will be important, and may also have to be monitored and controlled. In these cases, the light intensity compared with wavelength profile that the product is exposed to during manufacture, storage, and utilization should be specified.

It is therefore advisable to tabulate the major environmental stresses that an end-product will experience throughout its lifetime, and especially those that would be expected to impact the stability or performance of the active agent or delivery system.

Physical state and rheological properties. The end-product into which an active agent is going to be incorporated may be solid, semi-solid, or liquid. However, many commercial products are heterogeneous materials that contain domains with different physical states. For example, a capsule may have a solid outer shell and a liquid core. Similarly, a snack bar may be solid at the macroscopic level, but it may contain micro-domains that are gaseous (air pockets), liquid (oil droplets), amorphous (glassy carbohydrate regions), or crystalline (sugar, salt, or fat crystals). Consequently, it may be important to understand the physical state of the different domains within the product that the delivery system will be incorporated into, as well as the composition of these different domains. This information may help to design a colloidal delivery system that should be located within a specific region within an end-product.

The rheological properties of the overall material and of the various domains within it may also play an important role in determining the functional attributes and sensory properties of the end-product. For example, a capsule, tablet, or pill may have to be hard enough to resist fracture or erosion during storage and transport, but not so hard that it cannot be broken down after ingestion. Similarly, a food product may be expected to have certain desirable rheological attributes that are essential for its processing, preparation, or sensory perception. For example, a soft drink should be a low-viscosity liquid, a yogurt should be a viscoelastic gel, and a breakfast cereal should be a crispy solid. The rheological properties of the end-product should therefore be carefully specified, and then any delivery system that is utilized to incorporate an active agent should be specifically designed so that it does not adversely alter these properties. A brief overview of some of the most important rheological attributes of different kinds of materials that might comprise end-products is given below (Macosko 1994; Larsson 1998):

- *Solids*: The rheological properties of solids are typically determined by measuring their stress compared with strain profile using a suitable rheometer. These measurements provide information about the elastic modulus, breaking stress, and breaking strain of the material.
- *Semi-solids*: Many materials exhibit both solid-like and liquid-like properties, such as gels, spreads, and pastes, and they can be classified as *plastic* and/or *viscoelastic* materials. A plastic

material behaves like a solid below a critical applied stress (the yield stress), but it behaves like a liquid above this stress. This type of material can be characterized by an elastic modulus, yield stress, and apparent viscosity. A viscoelastic material simultaneously displays both solid-like and liquid-like properties simultaneously, and it can be characterized by a complex elastic modulus, such as a frequency-dependent storage and loss modulus. The rheology of semi-solid materials can be measured using either compression or shear rheometers.

- *Liquids*: The rheological properties of liquid materials are usually characterized by measuring the shear stress compared with shear rate using a viscometer, with the slope of this curve being the viscosity. For ideal liquids, the shear stress is proportional to the shear rate, and a single viscosity can be used to describe their rheological behavior. For nonideal liquids, the apparent viscosity may either increase (shear-thickening) or decrease (shear-thinning) when the shear rate is increased, and it may depend on the length of time that the shear stress is applied. In this case, the viscosity at a particular shear rate and time is referred to as the apparent viscosity.

Careful characterization and specification of the rheological properties expected in the end-product is therefore required. For example, for a liquid product it may be important to specify the range of viscosities that are deemed acceptable for a desirable end-product with the required physicochemical, sensory, and functional attributes. In general, information about product rheology is important for several reasons (Larsson 1998; McClements 2015):

- *Textural and Sensory Properties*: Incorporation of the active agent into the product should not alter the desirable textural or sensory properties of the final product. For example, the incorporation of relatively large particles (>50 μm) into a food product may make it appear rough or gritty in the mouth. Moreover, the incorporation of a high concentration of colloidal particles may adversely increase the viscosity of a fluid product.
- *Stability*: Colloidal delivery systems contain particles that may cream or sediment due to gravity, which often leads to undesirable product appearance and to an uneven distribution of the active agent throughout the product. If a product is solid or highly viscous, then gravitational separation will not be a big issue because the particles will be trapped in place. However, if the product is a low viscosity liquid (such as a beverage), then the particles may be highly prone to creaming or sedimentation. In this case, it may be necessary to use colloidal particles that have small dimensions or good density-matching to avoid gravitational separation.
- *Molecular Transport*: The diffusion of molecules within a product depends on the rheological properties of the different phases. This process may impact the retention of an encapsulated active agent during storage, or it may influence the rate at which different constituents in a system come into contact and interact with each other (for example, a bioactive lipid and pro-oxidant). Molecular diffusion will also impact the release of active agents from colloidal particles. Consequently, it is often important to characterize the impact of the rheological properties of the different phases in a delivery system and end-product on molecular transport processes. It is important to distinguish between the macro- and micro-rheology of the system. The macro-rheology reflects the rheological characteristics of the system on the macroscopic scale, whereas the micro-rheology reflects the rheology experienced by molecules or particles on the small scale. As an example, small molecules may diffuse through a porous gel almost as quickly as through pure water, even though the macro-viscosity of the system is many orders of magnitude higher than that of water.

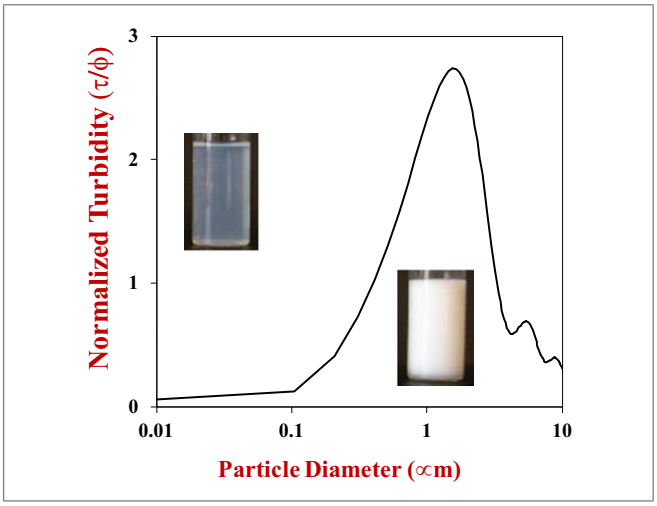

Figure 7–The optical properties of a colloidal dispersion depend on the size of the particles relative to wavelength of light. Here, the normalized turbidity (turbidity/disperse phase volume fraction) is plotted against particle size for oil-in-water emulsions.

Optical properties. The optical properties of pharmaceutical, food, personal care, and cosmetic products play a key role in determining consumer acceptability and desirability. Consequently, incorporating an active agent into a commercial product must not adversely affect its appearance. Colloidal delivery systems may impact the optical properties of products due to their ability to scatter and absorb light. The particles in a colloidal suspension scatter light by an amount that depends on their concentration, size, and relative refractive index (McClements 2002; Michels and others 2008). Typically, particles scatter light relatively weakly when their dimensions are much smaller or greater than the wavelength of light (380 to 780 nm), but they scatter light strongly when their dimensions are similar (Figure 7). If the final product is supposed to be optically transparent, then it will be important to use colloidal particles that do not scatter light strongly, which usually means that their diameters must be less than about 50 nm (Wooster and others 2008). Alternatively, it may be possible to match the refractive index of the colloidal particles to those of the surrounding matrix by changing their composition (Sun and others 2005). Colloidal delivery systems can also alter the color of commercial products when they contain any components that selectively absorb light in the visible region (Chantrapornchai and others 1998; Chantrapornchai and others 1999). This color change may limit their application in certain products. For example, the addition of a brown-colored delivery system to a white product (such as milk) may cause an undesirable alteration in its appearance. Consequently, it is important when designing colloidal delivery systems to take into account the desired optical properties of the final product. The optical properties can often be specified in terms of the absorbance compared with wavelength profile (transparent products) or transmission compared with wavelength profile (opaque products), or by specifying the tristimulus color coordinates (such

Table 3a–Summary of some of the most important properties required in an end product.

Property	Requirements: Define range of acceptable values
Physical state	*Solid* – Define elastic modulus, breaking stress, and breaking strain. *Semi-solid* – Define elastic modulus, yield stress, viscosity. *Liquid* – Define apparent viscosity compared with shear strain
Optical properties	*Transparency*: Define turbidity or lightness required *Color* – Define absorbance profile or color coordinates
Stability	Define environmental stress ranges experience by product • pH • Ionic strength • Temperature
Functional attributes	Define desired retention and release profiles
Composition	Define ingredient requirements – All natural? Synthetic? Kosher? Vegetarian?
Economic factors	Define the required cost-in-use of the delivery system

as L*, a*, b*) (McClements 2002). Typically, it is important to specify the range of color coordinates that are acceptable in the end-product, and then to ensure that the incorporation of the delivery system does not cause the product appearance to move out of this range.

Stage 3: Delivery system specification

Once the properties of the active agent and end-product have been carefully defined, then it is necessary to specify the functional attributes required in any delivery system that would be suitable for the desired application (Table 3a and 3b).

Physical form and rheological properties. Depending on the requirements of the application, a colloidal delivery system may have to be formulated so that it can be utilized in a liquid, semi-solid, or solid form, for example, a low- or high-viscosity fluid, viscoelastic gel, or powder (Macosko 1994; Larsson 1998). The physical form that is most appropriate for a particular application depends on the nature of the end-product. For instance, if the end-product is a low-viscosity liquid (such as a soft drink or nutritional beverage), then the delivery system should be a liquid or a powder that rapidly dissolves and that does not increase the viscosity appreciably. Alternatively, if the end-product is normally a viscoelastic gel (such as a yogurt or hand cream) then the introduction of the delivery system should not adversely impact its desirable textural properties. Finally, if the end-product is a solid material (such as a pill or snack bar), then it may be necessary to use a liquid form of the delivery system that can be conveniently incorporated into the manufacturing process before the drying stage, or to use a powdered form that can be incorporated before or after drying. Consequently, it is important to specify the required physical form of the delivery system and its impact on the rheology of the end-product.

Optical properties. Colloidal delivery systems can be formulated so that they can be clear, turbid, or opaque depending on the size, concentration, and refractive index of the particles they contain (McClements 2002). The optical properties of the delivery system should therefore be carefully selected so that they are suitable for the final application. An optically transparent delivery system would be most appropriate for application in clear commercial products (such as fortified waters or soft drinks), whereas an optically opaque delivery system would be more suitable for application in opaque products (such as pills, milk, or dressings). The color of the delivery system may also be important. For many applications, it will be advantageous to have a neutral (whitish) appearance so that it will not affect the color of the final product. Consequently, it is important to quantify and specify the optical properties of the delivery system. For transparent delivery systems, this can be achieved by measuring the absorbance compared with wavelength profile using a UV-visible spectrophotometer. For opaque systems, this can be achieved by measuring the reflectance compared with wavelength profile or the tristimulus color coordinates (L^*, a^*, and b^* values). Experiments should therefore be carried out to determine the impact of incorporating the delivery system into the end-product on its optical properties. Some colloidal delivery systems can be ruled out for certain applications because they do not have the required optical characteristics. For example, an emulsion would not be suitable for application in a transparent soft drink because it would make the end-product look cloudy or opaque.

Stability characteristics. The stability characteristics of the delivery system should be compatible with the requirements of the commercial product that it will be incorporated into. Information about the range of pH values, ionic strengths, temperatures, ingredients, oxygen levels, and light exposure in the end-product should be determined as described in Section "Stage 2: End-product Definition". This information can then be used to specify the range of environmental conditions where the delivery system should remain stable.

Functional attributes. A colloidal delivery system may have to be designed to have specific functional attributes, which depend on the application. Some of the most common functional attributes that might be required are briefly discussed here:

- *Loading*: A delivery system has to be designed to carry a certain amount of active agent, which depends on the intended application. For example, a flavor compound may have to be present at a certain concentration to give the desired flavor profile, or a pharmaceutical may have to be present at a particular level to give the required health effect. Consequently, the amount of the active agent that should be present within the end-product, and within the delivery system, should be carefully specified. The amount of active agent that can be incorporated will depend on the loading capacity of the colloidal particles, namely, the maximum amount that can be encapsulated per unit mass of particles. Typically, one wants to have a high loading capacity of the active agent in the delivery system, so as to minimize the amount of carrier material required.
- *Protection*: The delivery system may have to be designed to protect an active agent from chemical degradation under a particular range of solution or environmental conditions (such as pH, oxygen, light, ingredient interactions, or temperature). Knowledge of the chemical stability characteristics of the active agent and the nature of the end-product matrix can be utilized to specify those conditions that a delivery system must be designed to prevent or inhibit degradation. Moreover, knowledge of the constituents in a system that impact the chemical degradation rate can be used to design a delivery system that is more effective at protecting a labile active agent. For instance, antioxidants may be incorporated into a delivery system containing an active agent that is susceptible to oxidation.

Table 3b–Example of desired physicochemical properties for a functional beverage that is fortified with curcumin.

Property	Requirements
Physical form	*Liquid* – The product should be an ideal liquid with a shear viscosity in the range 2 to 5 mPa s.
Optical properties	*Color and opacity* – The product should have a homogeneous creamy yellow appearance. The initial tristimulus color coordinates of the product should fall within the following ranges: L^* from 85 to 90; a^* from 4 to 5; b^* from 58 to 62. The reduction in the yellow color intensity (b^* value) should be less than 20% over 12-mo storage at 30 °C in the light.
Stability	The functional beverage should meet the following stability requirements. *Physical stability*: The product should not exhibit visible phase separation or an increase in mean particle diameter >20% during production, storage, or utilization.
Functional attributes	• The product should have a desirable tangy citrus flavor. • The product should be designed to protect curcumin in the GIT, so that the amount reaching the blood is from 5 to 10 nmol/L.
Critical compositional factors	The product should be fabricated entirely from natural plant-based ingredients. The product also contains the following compositional attributes: • Natural buffers for pH control (pH 6 to 7) • Minerals for flavor and nutrition (Ionic strength around 90 to 110 mM) • Soluble dietary fiber for texture, mouthfeel, and nutrition (1% anionic or neutral polysaccharides)
Critical processing conditions	The product should remain stable after thermal processing at 75 °C for 15 s (HTST). The product should remain stable after exposure to high shear mixing conditions (500 rev/min for 5 min).
Critical storage conditions	The product should remain physically and chemically stable when stored at temperatures ranging from 0 to 45 °C for 12 mo.
Economic factors	The end product should cost less than 15 cents per unit.

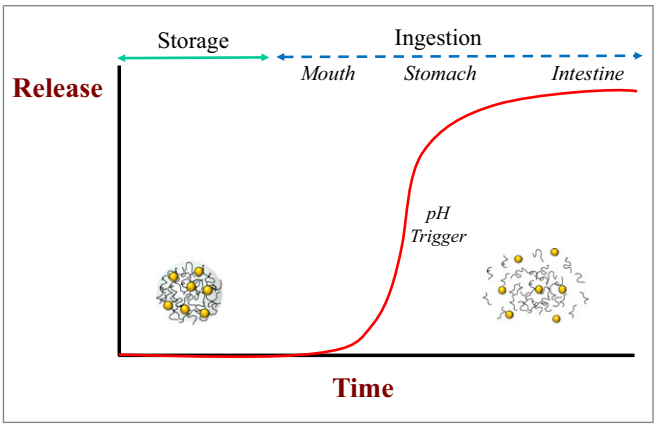

Figure 8–Schematic representation of different types of release profile that may be obtained for an active ingredient from a delivery system.

- *Retention and release profile*: The delivery system usually has to be designed to ensure that the active agent remains trapped inside the colloidal particles until a specific set of solution or environmental conditions is encountered, and then the active agent is released (Figure 8). It is therefore important to specify the range of conditions where the active agent should remain encapsulated, and the range where it should be released. This often involves specifying a particular trigger for release, such as time, temperature, pH, ionic strength, or enzyme activity. Moreover, it may involve specifying a particular release compared with time profile for the active agent, such as sustained or burst release. This information can then be used to establish particle properties that will lead to this release profile.
- *Dispersibility*: The delivery system may have to be dispersed into different types of end-products, which may vary in their physical state, pH, ionic strength, composition, and temperatures. It is usually important that the delivery system will rapidly and intimately mix with the environment that it is incorporated in. Consequently, it may be important to specify the required dissolution or dispersion times of the delivery system under environmental conditions that are applicable to the particular application.

Stage 4: Particle specification & delivery system selection

Once the desired physicochemical and functional attributes of the delivery system have been established, it is then necessary to select or design an appropriate system that contains colloidal particles with properties that meet the required specifications. Usually, it is advantageous to identify the simplest and least expensive colloidal delivery system that has the characteristics required to meet this goal. If this system does not provide the required attributes, then a more sophisticated one can be utilized, provided the additional costs can be justified. Some of the most important particle characteristics that can be manipulated to obtain the desired delivery system attributes are discussed briefly here (Table 4a and 4b).

Particle composition. The composition of the particles in a colloidal delivery system should be carefully controlled to give the required physicochemical and functional attributes. Colloidal particles can be assembled from a variety of different building blocks, including surfactants, lipids, polymers, water, minerals, antioxidants, and cross-linking agents. Consequently, there is considerable scope in tailoring the composition of colloidal particles for specific applications. Nevertheless, the types and levels of components selected must be consistent with government regulations pertaining to the end-product, be readily available, and be economically viable. These aspects are often neglected in the scientific literature when developing colloidal delivery systems for particular applications. Numerous other factors also influence the selection of a specific particle composition. First, there may be marketing demands that favor the inclusion of some components and the exclusion of others. For example, the food industry often prefers the utilization of natural plant-based ingredients because consumers perceive these to be "healthier" and more environmentally sustainable than synthetic or animal-based ones (McClements and Gumus 2016; McClements and others 2017). For similar reasons, there is a push towards excluding synthetic surfactants or solvents from many commercial products. Second, the production method used to fabricate a particular type of colloidal delivery system may limit the type of components that can be selected to assemble the particles. For example, micelles, microemulsions, and low-energy nanoemulsions are typically only fabricated from synthetic surfactants, whereas liposomes are typically only assembled from natural phospholipids. Third, the components used to fabricate the colloidal particles may be selected to provide specific physicochemical or functional attributes, such as density, refractive index,

Table 4a–Summary of the general properties required in a colloidal delivery system.

Property	Requirements
Physical form	*Liquid, Semi-solid, Solid*
Optical properties	Transparent, Turbid or Opaque – Define turbidity or lightness required Color – Define absorbance or color coordinates
Stability	Define environmental stress ranges pH Ionic strength Temperature
Functional attributes	Define retention and release profile
Composition	Define ingredient requirements – All natural? Synthetic? Kosher? Vegetarian?
Economic factors	Define the required cost-in-use of the delivery system

Table 4b–Summary of properties required in a colloidal delivery system needed to produce curcumin-loaded functional beverages.

Property	Requirements
Physical form	The delivery system can be a fluid or powder that rapidly disperses into an aqueous solution at ambient temperature (pH 6.5).
Optical properties	The delivery system should produce a final product that has a creamy yellow appearance at the intended usage level.
Stability	The functional beverage should meet the following stability requirements. *Physical stability*: The product should not exhibit visible phase separation or an increase in mean particle diameter > 20% when exposed to the following conditions: *Temperature*: It should remain stable after thermal processing at 75 °C for 15 s (HTST). It should remain stable when stored at temperatures ranging from 0 to 45 °C for 12 mo. *pH*: It should remain physically and chemically stable at pH values ranging from 6.0 to 7.0 when stored for 12 mo (30 °C). *Chemical stability*: The product should contain >1000 mg of active curcumin when stored for 12 mo (30 °C, pH 6.5).
Functional attributes	The curcumin should not degrade appreciable (<20%) during production, storage, and utilization. The curcumin should be protected in the GIT to ensure a relatively high bioavailability.
Composition	The product should be fabricated entirely from natural plant-based ingredients.
Economic factors	The delivery system should cost less than 2 cents per unit.

rheology, stability, retention, and release. For instance, starches, proteins, and lipids are digested in the upper GIT by amylases, proteases, and lipases, whereas dietary fibers are only digested in the large GIT by enzymes excreted by colonic bacteria. Consequently, components may be selected so that the colloidal particles break down and release their payload at a specific location within the GIT. Fourth, some components used to fabricate colloidal particles have antioxidant properties, such as some proteins and phospholipids, which can be utilized to stabilize chemically labile active agents.

Particle concentration. The concentration of particles present in a colloidal delivery system impacts its physicochemical and functional attributes, and so it is important to specify the level that should be present (McClements 2015). Typically, one wants to have a relatively high particle concentration in the delivery system itself, as this will reduce transport and storage costs. On the other hand, one typically wants to use as little of the delivery system as possible in the end-product, as this will reduce ingredient costs and any potentially undesirable effects of the delivery system on the end-product properties. Both of these goals can be achieved by preparing concentrated colloidal delivery systems that have a high loading capacity, and that can easily be dispersed into the end-product.

The concentration of particles in a colloidal delivery system depends on the method used to prepare it, and may vary widely from method-to-method. For example, relatively high particle concentrations can be achieved in nanoemulsions and emulsions produced by homogenization (>50%), whereas only low particle concentrations can be achieved in polymer nanoparticle suspensions produced by antisolvent precipitation (<5%). Nevertheless, the particle concentration can often be altered after the formation of a delivery system. For example, particle concentration can be increased using evaporation, centrifugation, or filtration methods or it can be decreased using dilution methods. In addition, a colloidal delivery system can be converted into a powdered form using methods such as spray-drying or freeze-drying, and then dispersed to the required level in the end-product. The manufacturer should therefore specify the required particle concentration in the colloidal delivery system and in the end-product, and also select a colloidal delivery system that can achieve this goal.

Particle morphology. The shape of the particles in a colloidal delivery system may impact its functional performance by altering its optical, rheological, stability, and release characteristics, and so it may be important to select a delivery system that has a specified particle shape. Different particle shapes can sometimes be produced by controlling the components and processing methods used to manufacture them. For instance, biopolymer microgels with different shapes can be created by applying mechanical forces to a system during the particle formation and gelation process (Wolf and others 2000; Norton and Frith 2001). However, in other cases it is difficult to control the particle shape. For instance, particles in many colloidal delivery systems tend to be spherical because of strong interfacial tension effects (the Laplace pressure), such as in microemulsions, nanoemulsions, and emulsions (Israelachvili 2011).

It may also be important to control the internal structure of the particles in a colloidal delivery system, which can often be achieved by selecting appropriate particle formation or post-formation methods (McClements 2014). For example, it may be desirable to select a colloidal delivery system that contains homogeneous, core-shell, dispersion, or clustered particles depending on the application (Figure 2). This type of system can be created using the structural design principles described in Section "Complex Delivery Systems." However, again it should be stressed, that it is usually important to identify the simplest, cheapest, and most robust solution to a problem. For many applications, spherical homogeneous particles are suitable to encapsulate, protect, and deliver active agents, and these relatively simple delivery systems should be the first option examined.

Particle dimensions. The dimensions of the particles in a colloidal delivery system have an important impact on its physicochemical, sensory, and functional properties, such as appearance, texture, stability, interactions, retention, release, and bioavailability (McClements 2015). Consequently, a delivery system should be selected that has the particle size characteristics required to meet the end-product requirements. The dimensions of the particles in a colloidal dispersion are usually characterized by the particle size distribution, mean particle diameter, and polydispersity index. Colloidal particles may vary considerably in their mean diameters (around 10 nm to 1000 μm) and polydispersity indices (around

0.1 to 1) depending on the nature, composition, and fabrication method used.

In colloidal particles that have complex internal morphologies, the dimensions of the different phases may also influence their functional attributes, such as shell thickness, core diameter, or the diameter of any dispersed particles. For instance, the release of an encapsulated substance from a core-shell particle is influenced by both the shell thickness and the core diameter (Baker 1987).

It is important to select a colloidal delivery system with particle dimensions that give the required physicochemical and functional attributes in the end-product. Some of the key attributes of delivery systems that are highly dependent on particle size are briefly discussed here:

Gravitational separation: The velocity (v) at which a particle moves due to gravity is proportional to the square of the particle diameter, which is described by Stokes' law (McClements 2015):

$$v = -\frac{g\,d^2\,(\rho_2 - \rho_1)}{18\eta_1} \tag{1}$$

Here, g is the gravitational constant, d is the diameter of the colloidal particle, ρ is the density, η is the shear viscosity, and the subscripts 1 and 2 refer to the surrounding liquid and the colloidal particles, respectively. The sign of v determines if the colloidal particles move upwards (+) due to creaming or downwards (–) due to sedimentation. Stokes' law is particularly useful for determining the particle size that is required for certain applications. Colloidal particles dispersed in water are highly susceptible to gravitational separation when their diameter exceeds about 500 nm, that is, oil droplets will cream >1 mm/day. Consequently, for low-viscosity end-products it may be necessary to ensure that the particle size is appreciably below this value to ensure good stability to creaming or sedimentation. Conversely, this factor is much less important for highly viscous, gelled, or solid products because particle movement is severely restricted by the surrounding matrix.

Appearance: The appearance of a final product is strongly dependent on the size of the particles it contains (McClements 2002). It is therefore important to specify the particle size characteristics required in the colloidal delivery system to ensure that the end-product has the appropriate optical properties, such as clear, cloudy, or opaque. A calculation of the change in turbidity with particle size is particularly useful for selecting a colloidal delivery system with the required appearance (Figure 7). Typically, a particle diameter less than about 50 nm is required to produce a colloidal dispersion that is optically transparent because light-scattering is relatively weak when the particle dimensions are much less than the wavelength of light (Wooster, Golding and Sanguansri 2008). Conversely, a particle diameter around 500 nm will lead to a system that scatters light strongly so that it appears optically opaque or turbid depending on particle concentration.

Textural perception: The sensory perception of particles in the mouth or skin depends on their dimensions. Typically, colloidal dispersions containing particles smaller than about 50 μm in diameter are perceived as being smooth in the mouth, whereas those containing larger ones may be perceived as being rough or gritty, although this critical size depends on the nature of the particles (Engelen and others 2005, Lopez and others 2016). It may therefore be important to select a colloidal delivery system that has particle size characteristics that give the desired textural attributes.

Retention and Release: The retention and release profile of an active agent from a colloidal particle is highly dependent on its dimensions (Siepmann and Siepmann 2011, Siepmann and Siepmann 2012). Typically, the smaller the particle size, the faster the tendency for the active agent to be released because of the shorter diffusion length. Theoretical equations are available to predict the release profile of active agents from particles under different conditions, and these are particularly useful for specifying the appropriate particle size required for a particular application (Arifin and others 2006; Mathias and Crison 2012; Siepmann and Siepmann 2012). The following simple expression is appropriate for predicting the time required for half of an active agent ($t_{1/2}$) to be released from a homogeneous sphere dispersed in a well-stirred liquid (McClements 2014):

$$t_{1/2} = \frac{0.0146 d^2 K_{12}}{D} \tag{2}$$

Here D is the translational diffusion coefficient of the active agent through the colloidal particles, and K_{12} is the equilibrium partitioning coefficient between the particles and surrounding liquid. As an example, the $t_{1/2}$ times for the diffusion of a lipophilic active agent out of oil droplets dispersed in water ($K_{21} = 1000$; $D = 4\times10^{-10}$ m^2/s) is about 3.65 μs, 365 μs, 36.5 ms, 3.65 s, and 608 min for particles with diameters of 10 nm, 100 nm, 1000 μm, 10000 μm, and 100000 μm, respectively. These simple predictions show that nanoemulsions would give very rapid release of any encapsulated active agents, and would therefore be unsuitable for sustained release applications. In order to retard the release rate, it would be necessary to utilize much larger particles, such as polymer microgels.

Particle dimensions impact many properties of colloidal delivery systems and therefore it is often important to come to some compromise size that best meets the required specifications. For instance, reducing the size may improve the optical clarity and creaming stability of a nanoemulsion, but it may also lead to poor protection, low retention, and rapid release of an active agent. Consequently, some intermediate particle size may be preferred. Alternatively, it may be possible to utilize combined systems, such as small nanoemulsion droplets embedded within larger polymer microgels, to obtain the required functional attributes.

Particle physicochemical properties. The functional performance of colloidal delivery systems depends on the physicochemical properties of the materials used to construct the particles, such as their density, refractive index, and rheology (McClements 2014). For example, particle density effects gravitational separation, refractive index effects light scattering, and rheology effects release rates. Consequently, it is usually important to select ingredients and processing conditions that will give appropriate physicochemical properties in the particles. For example, it may be desirable to create particles that have the same density or refractive index as the surrounding matrix to prevent gravitational separation or to have an optically transparent system, respectively. It is therefore important to select a colloidal delivery system that can be fabricated with the required physicochemical properties. The ability to modulate these properties is highly dependent on the nature of the delivery system.

Particle charge. The electrical properties of the particles in a colloidal delivery system impact many of its functional properties, and they should therefore be clearly specified (McClements 2007). The electrical properties of colloidal particles are usually characterized by the ζ-potential, which is the electrical potential at the "shear plane," namely, the region where counter-ions remain strongly attached to the particles as they move in an applied electrical field (Hunter 1986; Israelachvili 2011). The particle charge

may affect numerous properties of a delivery system: (i) *physical stability* – the electrostatic repulsion between particles may inhibit particle aggregation; (ii) *chemical stability* – a positively charged interface may repel cationic pro-oxidants (such as Fe^{2+} or Fe^{3+}); (iii) *ingredient interactions* – positively charged colloidal particles may interact with negatively charged components in an end-product; (iv) *adsorption* – cationic colloidal particles may stick to anionic surfaces in containers, the mouth, or the GIT. Consequently, it may be important to specify the desired electrical potential that the colloidal particles should have to ensure their proper performance in the end-product.

Particle interactions. The particles in a colloidal delivery system may interact with other components in their surroundings, for example, due to particle-particle, particle-surface, or particle-ingredient interactions. The most important colloidal interactions are van der Waals, electrostatic, steric, depletion, hydrogen bonding, and hydrophobic interactions (Israelachvili 2011). These colloidal interactions vary in their sign (attractive to repulsive), magnitude (strong to weak), and range (long to short). The colloidal interactions are mainly determined by particle properties (such as refractive index, dielectric constant, interfacial charge, and interfacial thickness), solution conditions (such as pH and ionic strength), and environmental factors (such as temperature). It is usually important to establish the major types of interactions that may occur in a particular colloidal delivery system and within the end-product, and then to control them so as to ensure the required stability and functional attributes.

Loading characteristics. It is important to specify the loading characteristics that are required for a colloidal delivery system for a particular application, that is, how much active component per unit mass of particles is present (McClements 2014). The level required will vary considerably depending on the nature of the active agent and the final application. For example, a relatively low level of active agent (a few ppm) may be required for some intense flavors, whereas a relatively high level (20000 ppm) may be required for ω-3 fatty acids. The loading characteristics depend on the maximum amount of the active agent that can be loaded into the colloidal particles, as well as the level of the colloidal particles that can be successfully incorporated into the end-product without adversely affecting its properties. The loading characteristics of colloidal particles vary widely depending on their composition and structure. The loading characteristics of a delivery system can be defined in terms of the loading capacity (LC) and encapsulation efficiency (EE) (McClements 2014). The LC is the percentage of active agent that is present within the colloidal particles:

$$\mathrm{LC} = 100 \times m_A/m_P \quad (3)$$

Here m_A is the mass of the active and m_P is the total mass of the colloidal particles (active agent + particle). LC may vary from around zero to 100% depending on the nature of the active agent and colloidal particles. For instance, the LC of a hydrophobic active agent may be <5% in a surfactant micelle but more than 90% in an emulsion or nanoemulsion.

The EE is defined as the percentage of the active agent that actually ends up inside the colloidal particles (rather than outside) after preparation:

$$\mathrm{EE} = 100 \times m_{A,E}/m_{A,T} \quad (4)$$

Here $m_{A,E}$ is the mass of encapsulated active agent, and $m_{A,T}$ is the total mass of active agent in the system (encapsulated + nonencapsulated). The EE may range from zero to 100% depending on the nature of the active agent, colloidal particles, and preparation procedure used. For example, close to 100% of a hydrophobic active agent (such as fish oil) is present inside emulsions and nanoemulsions, but less than 50% of a hydrophilic active agent (such as a protein) may be encapsulated in the interior of liposomes.

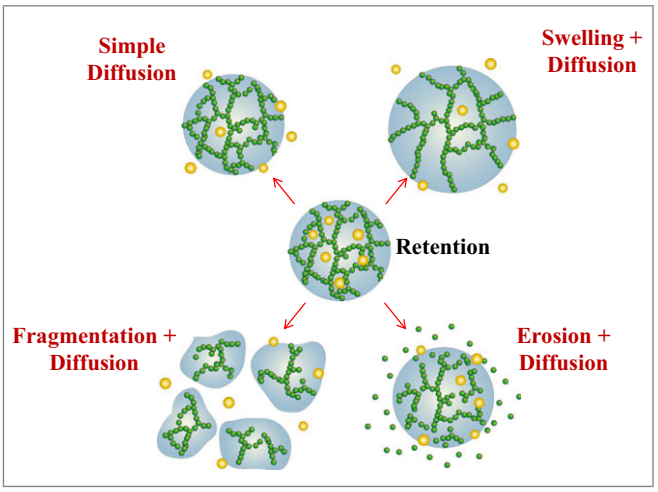

Figure 9–Some common physicochemical mechanisms responsible for release of active ingredients: diffusion; swelling; dissolution/erosion; and fragmentation.

The manufacturer should specify the LC and EE that is required for the specific application, and then select a delivery system that contains colloidal particles that meet these requirements.

Retention and release characteristics. Another important characteristic of a colloidal delivery system that must be considered when it is stored or incorporated into a commercial product is its retention and release properties (Siepmann and Siepmann 2011; Siepmann and Siepmann 2012; McClements 2014). Retention is the ability of the delivery system to trap the active agent inside the colloidal particles until the time when it should be released, whereas the release profile is the change in the amount of active agent released over time (Figure 8). The desired release profile depends on the specific application, and it may be a prolonged, burst, or triggered release. A prolonged process is a gradual release of the active agent over an extended period, whereas a burst process is a rapid release of the active agent over a short time. The release of the active agent may occur over time, or it may occur in response to a specific environmental trigger, such as pH, ionic strength, temperature, light, or enzyme activity. The release of the active agent may occur due to various mechanisms, including diffusion, particle erosion, particle fragmentation, or changes in molecular interactions or pore size (Figure 9). Mathematical theories have been developed to model many of these release mechanisms (Grassi and Grassi 2005; Arifin and others 2006; Aguzzi and others 2010; Kaunisto and others 2011; Sackett and Narasimhan 2011; Peppas 2013). The identification of a relevant mathematical theory is often an important step in the design of colloidal delivery systems with appropriate retention and release characteristics. Once the model has been validated, it can be used to establish the impact of the active agent and particle properties on the release rate, such as pore size, particle dimensions, partition coefficients, solubilities, and diffusion coefficients. This knowledge can then be used to control the rate of release by judicious selection of ingredients and processing operations.

The *retention efficiency* (RE) is the percentage of active agent that remains within the colloidal particles after a specified storage time or treatment:

$$RE = 100 \times m_{A,E}(t) / m_{A,E}(0) \quad (5)$$

The *release level* (RL) is defined as the percentage of active agent that is released from the colloidal particles after a specified storage time or treatment:

$$RL = 100 \times m_{A,NE}(t) / m_{A,E}(0) \quad (6)$$

Here, $m_{A,NE}(t)$ is the mass of nonencapsulated (released) active agent at time t. RL may range from zero (none released) to 100% (all released) depending on the system. It should be noted that RL = 100 – RE.

An ideal colloidal delivery system should have a high LC, EE, RE, and an appropriate RL compared with time profile for the specific application. A formulator should therefore specify the required values for these different parameters for the particular application, and then identify particle characteristics that will lead to these properties. This process is greatly aided by utilizing a suitable mathematical model. As an example, the release of an active agent from a porous colloidal particle due to diffusion can be modeled using the following expression (Crank 1975):

$$\Phi = \frac{M(t)}{M(\infty)} = 1 - \frac{6}{\pi^2}\sum_{n=1}^{\infty}\frac{1}{n^2}\exp\left(-\frac{D_{gel}n^2\pi^2 t}{a^2}\right) \quad (7)$$

Here, Φ is the fraction of the active agent that has been released from the colloidal particles due to diffusion after a certain time t, $M(t)$, and $M(\infty)$ are the concentrations of the active agent within the colloidal particles at time t and at equilibrium, n is an integer, a is the radius of the colloidal particle, and D_{gel} is the diffusion coefficient of the active agent through the porous network inside the colloidal particles, which can be modeled using the following expression (Zhang and Amsden 2006; Chan and Neufeld 2009):

$$D_{gel} = D_w \exp\left(-\pi\left(\frac{r_H + r_f}{\xi + 2r_f}\right)\right) \quad (8)$$

Here, D_w is the translational diffusion coefficient of the active agent through pure water, r_H is the hydrodynamic radius of the active agent, r_f is the cross-sectional radius of the polymer chains that comprise the gel network inside the colloidal particles, and ζ is the diameter of the pores in the gel network. These expressions can be used to predict the influence of colloidal particle dimensions, pore size, and active agent size on the rate of release.

Specifying and selecting characteristics. Based on the requirements specified for the delivery systems, it should be possible to specify the required particle properties, such as particle composition, size, charge, and loading, retention and release characteristics. This knowledge can then be used to select the type of colloidal delivery system that is most suitable (for example, nanoemulsion, microemulsion, solid lipid nanoparticles, or polymer particles), and then to optimize the ingredients and processing method used to fabricate these particles.

Stage 5: Process specification

Once a suitable colloidal delivery system has been identified, it is necessary to develop a processing operation that is able to economically and reliably manufacture it at the scale required for commercial applications. Many of the delivery systems that have been described in the scientific literature are unsuitable for commercial utilization, since they are not economically feasible or cannot be reproduced on a large enough scale. The objectives of this stage are to identify a suitable manufacturing process, and then to establish the key variables that have an impact on the properties of the colloidal particles in the delivery system. These key variables are likely to be related to the nature of the raw materials used to fabricate the delivery system, as well as critical steps in the manufacturing process (such as hydration, mixing, homogenization, or thermal processing). The processing operation used will be highly dependent on the nature of the delivery system that has been identified; however, it is possible to make some general recommendations about factors that should be considered. Initially, simple small-scale experiments may be carried out in a laboratory to rapidly screen different systems, but then it will be necessary to determine whether these colloidal particles can be created on a commercial scale.

Ingredient quality: Critical ingredient attributes. Colloidal delivery systems are typically formulated from a variety of different ingredients, such as the active agent, polymers, surfactants, lipids, and minerals. These ingredients may vary considerably in their composition and quality, which may affect the formation, stability and functional attributes of the colloidal delivery system. Consequently, it is important to establish the relationship between ingredient properties and colloidal delivery system performance, and then specify ingredient quality attributes and/or to modulate the processing operations to ensure that the final product always has consistent properties.

Manufacturing steps: Critical processing attributes. A number of different manufacturing steps are typically required to fabricate colloidal delivery systems. As a specific example, the formation of nanoemulsions loaded with a lipophilic active agent is used. Initially, the active agent must be fully dissolved in the oil phase, while a hydrophilic emulsifier must be fully dissolved in the aqueous phase. If these components are not dissolved properly, then it may be difficult to form a stable delivery system. Consequently, appropriate dissolution times, temperatures, and mixing conditions must be established for each ingredient to be dissolved. The oil and aqueous phases may then be homogenized using a high-shear mixer to produce a coarse emulsion. The size of the droplets in a coarse emulsion can impact its subsequent homogenization, and so it may be important to ensure that the particle size distribution at this stage is appropriate. For example, the manufacturer might specify that the mean droplet diameter should be less than 5000 nm and the polydispersity index less than 0.3. The coarse emulsion is then passed through a mechanical homogenizer (such as a high-pressure homogenizer or microfluidizer) to decrease the droplet size. This stage is likely to be especially critical to the proper performance of the end-product. It may therefore be important to specify the particle size distribution characteristics that should be met, based on preliminary studies. For example, a manufacturer may specify that the mean droplet diameter should be between 90 and 100 nm, the polydispersity index should be less than 0.2, and less than 1% of the droplets should be larger than 1000 nm. Finally, the physicochemical properties of the nanoemulsion might be specified, for example, the viscosity should be between 8 and 10 mPa s, the turbidity should be less than 0.05 cm^{-1}, and no visible phase separation should be observed during a 12-mo storage period at 30 °C.

Stage 6: Performance testing

Once a suitable colloidal delivery system has been developed it is important to establish an appropriate range of analytical tools and testing protocols to ensure its quality.

Analytical tools. A wide range of analytical tools has been developed to characterize the properties of colloidal delivery systems, which have been reviewed in detail elsewhere (McClements and McClements 2016). In this section, only a brief overview is therefore given. A suitable range of analytical tools should be capable of measuring appropriate active agent properties (such as concentration or transformation), particle properties (such as composition, size, shape, aggregation state, and charge), physicochemical properties (such as optical properties, rheology, and stability), sensory attributes (such as appearance, mouthfeel, and texture), gastrointestinal properties (such as bioavailability and location of release), and biological effects (such as biomarkers or bioactivity). The particle size and aggregation state is often measured using dynamic (3 to 3000 nm) or static (100 nm to 1000 μm) light-scattering methods, or optical (>1000 nm) or electron (>10 nm) microscopy methods. Particle charge (ζ-potential) is usually measured using electrophoresis instruments that measure the direction and velocity that colloidal particles move in an applied electric field. The rheology of colloidal delivery systems and end-products can be measured using various types of mechanical rheometers, whereas their optical properties can be characterized using colorimeters or UV-visible spectrophotometers. The sensory attributes of delivery systems and end-products can be determined using trained or untrained panels. The gastrointestinal fate and biological effects of delivery systems can be monitored using simulated GIT models, cell culture models, animal feeding studies, or human feeding studies. It is therefore important to select the most appropriate range of analytical tools to adequately characterize the properties of the delivery system and end-product containing it.

Testing protocols. A number of different types of testing protocols may be utilized to characterize the performance of a delivery system depending on its intended purpose.

In-product tests. The simplest type of testing protocol is to measure changes in the properties of the delivery system after it is incorporated into an end-product that is subjected to environmental conditions that mimic those it would experience throughout its lifetime. This may simply involve removing a product at different stages of its production, storage, transport, or utilization and then measuring its properties, such as loss of active agent, change in particle size, or alteration in appearance. Alternatively, the compositional and environmental conditions that the delivery system might experience in the end-product can be recreated in the laboratory.

Accelerated screening tests. Commercial end-products are often required to have a prolonged shelf-life, which may extend to many months or even years. A manufacturer often wants to predict the expected performance of a delivery system or an end-product using accelerated screening tests, as it is impractical to wait until the product has been produced, stored, and transported before a default is detected. For this reason, short-term accelerated screening tests are often carried out that enable one to predict the long-term performance of the product. These tests may accelerate any instability mechanisms, for example by exposing the system to environmental stresses that promote instability, such as storing at elevated temperatures, applying mechanical forces, exposing to light, or adding pro-oxidants. Accelerated screening tests may also be used to determine the potential release of encapsulated active agents, for example, by adding hydrotropic components (Othman and others 2016) or mixed micelles (Yang and McClements 2013) to the aqueous phase surrounding the colloidal particles to increase the solubility of the active agent. Nevertheless, it is always important to establish that the accelerated screening test gives results that correlate well with the actual long-term stability of the system.

Table 5–Outline of possible stress tests that can be used to establish the range of conditions a colloidal delivery system will function appropriately. After each treatment, the sample would be analyzed to determine if its properties had changed.

Stress type	Stress conditions
High temperatures	• General: Hold sample at temperatures ranging from 20 to 90 °C for 20 min. • High-temperature short-time (HTST) pasteurization: Hold sample at 72 °C for 15 s • Low-temperature long-time (LTLT) pasteurization: Hold sample at 63 °C for 30 min • Ultra-high temperature (UHT) pasteurization: Hold sample at >135 °C for 1 to 2 s
Low temperatures	• Chilling: Hold sample at 4 °C for 1 wk • Freezing: Hold sample at –20 °C for 1 wk, then thaw
pH	• Store samples at pH values ranging from 2 to 8 for 24 h
Ionic strength	• Store samples under different ionic conditions for 24 h: 0 to 500 mM NaCl; 0 to 50 mM $CaCl_2$.
Mechanical stress	• Place sample in a higher shear mixer for 5 min
Ingredient interactions	• Add different levels of known ingredients to sample and store for 24 h

Environmental stress tests. It is often useful to subject a colloidal delivery system to a number of well-defined stress tests to establish the range of conditions where it functions properly, such as the range of pH values, ionic strengths, temperatures, and mechanical stresses that it can withstand. This information can then be used to ascertain the types of end-product that the colloidal delivery system can be successfully utilized within. The types of stress tests typically utilized to establish the performance of colloidal delivery systems have been reviewed elsewhere (McClements and McClements 2016). Some examples of stress tests that could be used to screen the range of environmental conditions under which a colloidal delivery system would remain stable are shown in Table 5.

Stage 7: System optimization

Finally, it should be stressed that the creation of an effective colloidal delivery system is an iterative process (Figure 10). It may be necessary to change the composition or processing operation based on the observed performance of the colloidal delivery system in the end-product. Consequently, one should continually monitor and record the properties of the delivery system and end-product throughout its life cycle, and make appropriate adjustments where possible based on knowledge of the factors that affect its properties.

Case study: Encapsulation of Curcumin in Functional Beverages

In this section, a specific example is used to highlight the potential advantages of the DbD approach for developing effective colloidal delivery systems. Curcumin is a natural compound found in the turmeric plant that has been showed to exhibit a wide range of beneficial health effects when consumed at sufficiently high quantities (Anand and others 2007; Heger and others 2014). Consequently, there is considerable interest in incorporating curcumin into foods, supplements, and pharmaceuticals. However, this is often challenging because of the inherent molecular and physicochemical attributes of this active agent, and so colloidal

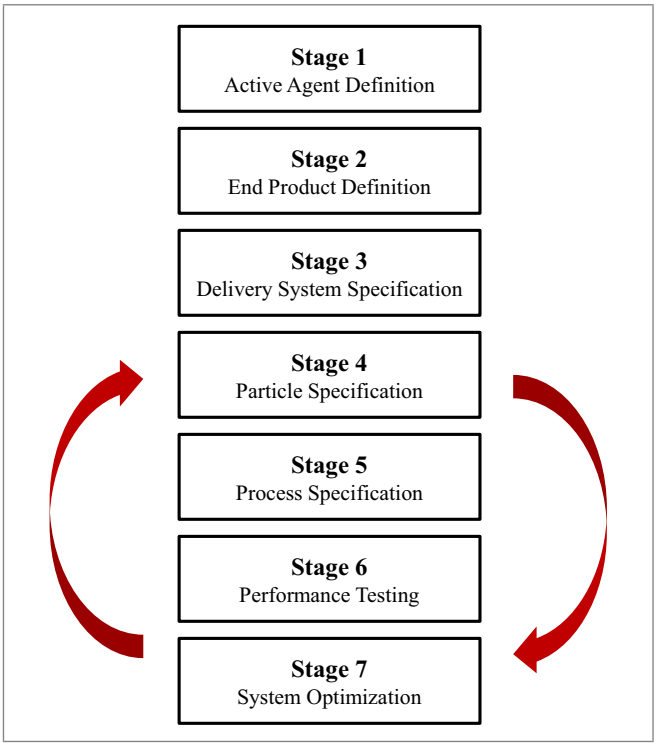

Figure 10–Schematic of different stages required in the development of colloidal delivery systems.

delivery systems are being designed to overcome these challenges. In this section, we consider the application of the DbD approach for the formulation of a functional beverage enriched with the bioactive molecule curcumin.

Stage 1: Active agent definition

The first stage in the development of an effective colloidal delivery system is to fully understand the nature of the active agent to be encapsulated, and to highlight potential challenges that need to be overcome when using encapsulation technologies. Curcumin is a relatively low molecular weight hydrophobic substance that has low water-solubility and is crystalline at ambient temperature (Table 2). Consequently, it cannot be incorporated into an aqueous-based functional beverage by simply mixing it with the other ingredients. Instead, it must be dispersed within some kind of colloidal particle that has a nonpolar interior capable of solubilizing the curcumin. One of the key challenges that must be overcome when incorporating curcumin into commercial end-products is its tendency to rapidly degrade in neutral or basic aqueous solutions (Figure 5). This problem can be partly overcome by ensuring that the curcumin is dispersed within a nonpolar environment (such as the interior of a colloidal particle) so as to reduce its direct contact with water. Other potential challenges that may limit the utilization of curcumin in certain products is that it has a yellow-orange color and a spicy taste profile.

Stage 2: End-product definition

Once the properties of the curcumin have been clearly defined, it is then important to define the properties of the end-product in which this active agent is going to be utilized. In this case, we assume that it will be a curcumin-fortified functional beverage, a drinkable product that is designed to provide health benefits. The specifications of the product are summarized in Table 3b. The product should have a creamy yellow appearance and a tangy citrus taste. It should be a liquid of relatively low-viscosity that remains physically and chemically stable throughout production, storage, transport, and utilization. It should also be designed to enhance the bioavailability of the curcumin, so that a claim can be made on the label. Finally, the product should be constructed entirely from food-grade plant-based ingredients that are widely available, since the product will be targeted at health-conscious consumers. These specifications will limit the type of colloidal delivery systems that are suitable.

Stage 3: Delivery system specification

Once the properties of the active agent and end-product have been defined, then it is necessary to specify the functional attributes required in the colloidal delivery system. Some of the most important attributes are summarized in Table 4b. In this case, the colloidal delivery system used should be physically and chemically stable over the range of conditions that the functional beverage experiences throughout its lifetime. For instance, it should be stable when exposed to certain thermal processing conditions, mechanical stresses, pH values, ionic strengths, and when stored under refrigeration or nonrefrigeration conditions. In addition, the colloidal delivery system should be stable in the presence of anionic or neutral polysaccharides (which could induce depletion or bridging effects) that are added as thickening agents. When incorporated into the end-product the delivery system should not adversely affect its desirable creamy yellow color, tangy citrus taste, or smooth mouthfeel.

Stage 4: Particle specification and delivery system selection

Once the desirable functional attributes of the colloidal delivery system have been defined, then it should be possible to specify particle properties that will lead to these characteristics. Since the end-product has a creamy appearance, it is possible to use particles that scatter light strongly, which means that most types of colloidal delivery system discussed in Section "Overview of Colloidal Delivery Systems" could be utilized. The end-product should have a relatively low viscosity (like milk) and so the colloidal particles selected should be stable to gravitational separation, which means that they should either be relatively small ($d < 300$ nm) and/or have good density matching ($\Delta\rho \approx 0$ kg m^{-3}). The product is expected to have a smooth mouthfeel, and so the diameter of the colloidal particles should be less than about 50 μm. Curcumin is a predominately hydrophobic molecule (logP > 4) that is chemically unstable when dispersed in neutral or alkaline aqueous solutions (Table 2), and so it would be advantageous to utilize colloidal particles with a hydrophobic interior. Alternatively, the product could be designed to have a fairly low pH. The curcumin should remain encapsulated within the mouth and stomach, but then be released in the small intestine so that it can be solubilized and absorbed. Hence, the delivery system should be designed to experience break down in the small intestine and release free fatty acids that can increase the solubilization capacity of the curcumin within the intestinal fluids. Curcumin is susceptible to chemical degradation under neutral and alkaline conditions, which may be inhibited by adding antioxidants. Consequently, it would be useful to incorporate a mixture of polar and nonpolar antioxidants that can retard curcumin degradation inside the delivery system. Finally, the colloidal particles should be fabricated from natural food-grade components, such as lipids, proteins, and carbohydrates. A number of colloidal delivery systems meet the above

criteria, including nanoemulsions, emulsions, solid lipid nanoparticles, biopolymer nanoparticles, and filled biopolymer microgels (Section "Overview of Colloidal Delivery Systems"). Ideally, the delivery system that is the simplest and cheapest to manufacture, but that provides the functionality required, should be used for this application. Emulsions and nanoemulsions are easy to prepare and can be used to convert curcumin into a water-dispersible form that is relatively stable, but they have fairly low loading capacities and poor chemical stabilities. These limitations can be overcome by using more sophisticated colloidal delivery systems, such as (i) mixtures of curcumin-loaded protein nanoparticles (to increase loading capacity and stability) and nanoemulsions (to ensure bioaccessibility); (ii) nanoemulsion droplets trapped inside biopolymer microgels (to improve stability); and (iii) nanoemulsion droplets coated with biopolymer layers (to improve stability). Nevertheless, the economic feasibility, environmental stability, and functional performance of these more sophisticated delivery systems must be established using the testing protocols discussed in Section "Testing Protocols".

Stage 5: Process specification

Once an appropriate delivery system has been identified, then a manufacturing process should be established that is capable of producing the colloidal particles on a scale that is required for the end-product. As an example, the fabrication of a colloidal delivery system consisting of a mixture of nanoemulsions and curcumin-loaded protein nanoparticles will be considered in this section (Zou and others 2016). A high-pressure homogenizer, such as a dual-channel microfluidizer, could be used to produce both the nanoemulsions and the biopolymer nanoparticles. In the case of the nanoemulsions, an oil phase containing digestible lipids (such as vegetable oil) could be homogenized with an aqueous phase containing a plant-based emulsifier (such as quillaja saponin). In the case of the curcumin-loaded biopolymer nanoparticles, an organic solvent containing the active agent and a hydrophobic protein (such as curcumin and zein dissolved in an ethanol solution) could be interacted with an aqueous phase containing a plant-based emulsifier (such as quillaja saponin). This process would lead to the spontaneous formation of curcumin-loaded zein nanoparticles stabilized by an emulsifier layer through an antisolvent precipitation method. Experiments would have to be carried out to optimize the system composition and homogenization conditions for the production of both types of particles. For example, the impact of oil-to-emulsifier ratio, oil type, emulsifier type, homogenization pressure, or number of passes through the homogenizer could be optimized for the nanoemulsions so as to produce small stable oil droplets.

Stage 6: Performance testing

A robust testing protocol should be established to determine the potential performance of the delivery system, and then to ensure that it meets the required production specifications. For example, the particle size distribution of both the nanoemulsions and biopolymer nanoparticles could be measured by dynamic light-scattering, while their electrical characteristics (ζ-potential) could be measured by particle electrophoresis. The manufacturer should specify a particular range of particle sizes and charges that the delivery system should have to give the required functional properties. The impact of environmental conditions on the stability of the colloidal delivery system could be determined by exposing it to different pH, ionic strength, temperature, ingredient, and mechanical conditions. The impact of the delivery system on the appearance, texture, and stability of the end-product could be determined by measuring the optical properties (colorimeter), rheology (rheometer), and phase separation (visual observation) of the functional beverage. The stability of the delivery system and end-product could be determined using in-product or accelerated stress tests (Section "Stage 6: Performance Testing").

Stage 7: System optimization

Analytical tests should be performed for each new batch of delivery system and end-product manufactured, and any product defaults can then be identified and rectified as quickly as possible. Moreover, it may be possible to further optimize the system by changing the composition or processing conditions to create a product with better stability characteristics or functional attributes.

Conclusions

There is growing interest in the utilization of colloidal delivery systems for the encapsulation, protection, and controlled release of active agents, such as drugs, nutraceuticals, vitamins, antimicrobials, antioxidants, colors, and flavors. However, many of the scientific articles published in this area do not consider the practical aspects of designing and fabricating colloidal delivery systems, so that the systems developed have little economic feasibility. This article develops a comprehensive and systematic approach for developing colloidal delivery systems for specific functional applications. This DbD approach begins by specifying the most important physicochemical properties and functional attributes required for both the active agent and the end-product. It then specifies the properties that any colloidal delivery system must possess to meet these requirements, which enables one to focus on those delivery systems that are the most appropriate for a particular application. Optimization of a commercially feasible fabrication method to manufacture the colloidal delivery system is then emphasized. Finally, the DbD approach stresses the need for developing a systematic approach to characterizing and refining the properties of the colloidal delivery system during the development and production stage. The application of this approach by food scientists should lead to the creation of more effective and commercially viable colloidal delivery systems for particular applications.

Acknowledgments

This material was partly based upon work supported by the National Institute of Food and Agriculture, USDA, Massachusetts Agricultural Experiment Station (MAS00491) and USDA, AFRI Grants (2014-67021, 2016–25147, and 2016–08782).

Conflict of Interest

The author states that he has no conflict of interest in this article.

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