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Araiza-Calahorra, A, Akhtar, M and Sarkar, A orcid.org/0000-0003-1742-2122 (2018) Recent advances in emulsion-based delivery approaches for curcumin: From encapsulation to bioaccessibility. Trends in Food Science and Technology, 71. pp. 155-169. ISSN 0924-2244

https://doi.org/10.1016/j.tifs.2017.11.009

Recent advances in emulsion-based delivery approaches for curcumin: From encapsulation to bioaccessibility

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Abstract

Background

Curcumin has been widely acknowledged for its health-promoting effects. However, its application is often limited by its poor water solubility and biochemical/ structural degradation during physiological transit that restricts its bioavailability. Emulsion based approaches have attracted the most research attention to encapsulate curcumin and improve its stability, bioaccessibility and bioavailability.

Scope and approach

This review summarizes the recent advances in application of different oil-in-water emulsion-based approaches, such as, conventional emulsions (surfactants-, protein- and protein-polysaccharide-stabilized emulsions), nanoemulsions, and Pickering emulsions that have been specifically used to deliver curcumin. Particular emphasis is given to factors affecting curcumin solubility, change in crystalline structure of curcumin upon dispersion and encapsulation efficiency. Changes in the droplet size and emulsion stability during in vitro oral-to-gastrointestinal digestion are discussed, with clear focus on the bioaccessibility of the encapsulated curcumin.

Key findings and conclusions

Key factors that influence curcumin delivery include emulsion droplet size, oil composition, volume fraction, dispersion conditions of curcumin in the oil phase and the type of interfacial materials. Nanoemulsions have been the preferred choice for delivery of curcumin up to now. Although scarce in literature, emulsions stabilized by edible Pickering particles as shown by recent evidence are effective in protecting curcumin in an in vitro gastrointestinal setting due to their high coalescence stability. Further studies with emulsions stabilized by food-grade particles and accurate tracking of the physiological fate (in vitro to human trials) of different emulsion-based delivery vehicles are essential for rational designing of curcumin-rich functional foods with high bioaccessibility.

Keywords

Curcumin; Pickering emulsion; Nanoemulsion; Encapsulation efficiency; Bioaccessibility

1 Introduction

Curcumin is a natural low-molecular-weight polyphenolic compound found in the rhizome of the perennial herb, turmeric (Curcuma longa) (Sharma, Gescher, & Steward, 2005). Curcuma longa is comprised of 3–5% curcuminoids, with the four main types being curcumin (77%), demethoxycurcumin (17%), bisdemethoxycurcumin (3%), and cyclocurcumin (Goel, Kunnumakkara, & Aggarwal, 2008; Heger, Golen, Broekgaarden, & Michel, 2014). Curcumin has a molecular weight of 368.37 g mol^{-1} and a melting point of 183 ^{o}C (Tapal & Tiku, 2012). In the last few decades, curcumin has gained significant research attention owing to its wide range of health-promoting properties, such as anti-inflammatory, anticarcinogenic, and antioxidant activities (Ak & Gülçin, 2008; Fujisawa, Atsumi, Mariko Ishihara, & Yoshinori Kadoma, 2004; Selvam, Jachak, Thilagavathi, & Chakraborti, 2005). Hence, research has been conducted extensively in recent years to design food-based encapsulation vehicles that can deliver curcumin effectively in targetted physiological sites.

The main challenge in delivering curcumin effectively in human physiology is that curcumin is a highly lipophilic compound, which limits its absorption in the human body. Besides its poor water solubility, the relatively high rate of metabolic degradation during physiological transit, inactivity of the metabolic end-products, and rapid elimination from the body reduce the bioavailability of curcumin (Bansal, Goel, Aqil, Vadhanam, & Gupta, 2011). To overcome these challenges and to improve the bioavailability of curcumin upon ingestion, many studies have attempted to encapsulate curcumin using delivery systems, such as hydrogels (Gong, et al., 2013), nanoparticles (Bisht, et al., 2007), and liposomes (Hasan, et al., 2014).

Particularly, food colloid scientists have shown that emulsions can be facile templates to encapsulate lipophilic curcumin and improve its stability and bioavailability by manipulating the bioaccessibility of these colloidal delivery systems. Essentially, two main emulsion-based approaches have been used to deliver curcumin: emulsion-based delivery systems and excipient emulsion systems.

In emulsion-based delivery systems, the isolated curcumin is solubilized first within the oil phase of an oil-in-water emulsion during the formation of the emulsion. Preliminary evidence has suggested that emulsion-based delivery systems can be used to encapsulate curcumin to increase its oral bioaccessibility, permeability, and resistance to metabolic processes during physiological transit (Zhang & McClements, 2016). On the other hand, in excipient emulsion systems, the curcumin is kept within its natural environment (used in its original form, such as a powdered spice) and is co-ingested with an oil-in-water excipient emulsion. Detailed information about excipient emulsion systems that have been used to deliver curcumin can be found in recent literatures (McClements, et al., 2016; Zhang & McClements, 2016; Zou, et al., 2015b; Zou, et al., 2016). For excipient emulsion systems the curcumin-free emulsion needs to be consumed with a curcumin-rich food or food ingredient (Zhang & McClements, 2016), whereas, for emulsion-based delivery systems, the curcumin-loaded emulsion can be used as a sole nutraceutical application, the latter has attracted considerable research attention.

There has been a strong upsurge in research efforts, in recent years, in delivering curcumin using emulsions of different sizes, structures and properties, and assessing the ability of these emulsions to protect curcumin during in vitro oral-to-gastrointestinal digestion. The droplet size distribution and the microstructure of the emulsions have been tailored to improve the bioaccessibility of curcumin. To the best of our knowledge, there is no literature source that has systematically reviewed the emulsion-based delivery systems that have been used for encapsulating curcumin and identified the specific factors affecting the stability of the encapsulated curcumin pre- and post-ingestion as well as its bioaccessibility. Such information is crucial in order to expolit emulsion-based approaches to design next generation curcumin-rich functional foods, functional ingredients and pharmaceutical applications.

Hence, the aim of this review is to provide an update of the recent advances in emulsion-based approaches for the delivery of curcumin. We have specifically focussed on emulsion-based delivery systems, such as, conventional oil-in-water (O/W) emulsions, Pickering emulsions, and nanoemulsions stabilized by a surfactant, protein-polysaccharide conjugates and complexes, solid particles that have specifically been used to encapsulate curcumin. Firstly, we have discussed the structure and physicochemical properties of curcumin, including research work at our own laboratory, which are key parameters for selecting the appropriate delivery approach. Specifically, we have discussed the

solubility and crystalline structure of curcumin in different solvents in order to enable the optimal selection of the oils and/or fatty acids, and identified the key challenges encountered in poor dispersability. Secondly, we have discussed the specific factors in designing the emulsion-based systems that affect the loading and encapsulation efficiency of curcumin, droplet size change after curcumin incorporation, and in vitro gastrointestinal stability of the encapsulated curcumin. We have critically analyzed the release properties and bioaccessibility of curcumin in oral, gastric and intestinal regimes. Finally, we have highlighted the key research gaps and future trends in the research domain of delivery and bioaccessibility of curcumin using emulsion-based approaches.

The literature search was systematically conducted using three key search engines: ScienceDirect, PubMed and American Chemistry Society (ACS). In addition, 'Google Scholar' was also used to search for publications and additional information. Keywords used were 'curcumin', 'curcumin structure', 'curcumin emulsion(s)', 'curcumin nanoemulsion', and 'curcumin Pickering emulsion'. The initial selection of publications was made on the basis of the title of the publication, keywords, and abstract screening. Full-text articles were analyzed for inclusion in the review. The reference list of each paper was carefully checked to identify any relevant previous studies and full-text screening was conducted for the same.

2 General aspects of curcumin

2.1 Structure of curcumin

Curcumin is a yellowish powder, with an ordered crystal structure (Rachmawati, Edityaningrum, & Mauludin, 2013; Zhao, et al., 2015). From a structural viewpoint, curcumin is comprised of two aromatic rings with methoxyl and hydroxyl groups in the ortho position with respect to each other (Figure 1). The aromatic rings are connected through seven carbons that contain two α,β-unsaturated carbonyl groups. As a result, curcumin exists in three possible forms, two isomers in an equilibrating keto-enol tautomeric form, and a β-diketonic tautomeric form (Payton, Sandusky, & Alworth, 2007). Under slightly acidic and neutral conditions, the keto-form of curcumin dominates (Jovanovic, Steenken, Boone, & Simic, 1999). However, when dissolved in ethanol at 70 ^{o}C in the dark and in

129 aqueous solutions at pH > 8, curcumin exists primarily in its enolic form; the latter provides its radical-
130 scavenging ability (Jovanovic, et al., 1999; Kolev, Velcheva, Stamboliyska, & Spiteller, 2005).

131 In crystalline phase, the molecule prefers the enol configuration stabilized by strong
132 intramolecular hydrogen-bonding (H-bonding) (Tønnesen, Karlsen, & Mostad, 1982). However, as a
133 result of this intermolecular H-bonding, the molecule loses its planarity (Kolev, et al., 2005).
134 Polymorphism of crystal structures of curcumin depends on the crystallization conditions. Curcumin
135 crystals can adopt different shapes, such as monoclinic (acicular), orthorhombic (rice seed like), and
136 amorphous (Liu, Svärd, Hippen, & Rasmuson, 2015; Mishra, Sanphui, Ramamurty, & Desiraju, 2014;
137 Sanphui, Goud, Khandavilli, Bhanoth, & Nangia, 2011)

138 Using scanning electron microscopy (SEM), to analyze curcumin particles, in our laboratory has
139 revealed interesting morphological characteristics, that was dependent on the solvent in which curcumin
140 was dispersed. Figure 2a presents a SEM image of the curcumin particles dispersed in methanol.
141 Curcumin showed a long plate-like morphology of around 20-31 μm length and aspect ratio (length-to-
142 width) varied from 4:1 to 6:1, which is in agreement with previous reports (Kurniawansyah,
143 Mammucari, & Foster, 2017; Thorat & Dalvi, 2014, 2015). Formation of the repeated stacks of
144 curcumin plates as observed in Figure 2a has also been described by other authors as an end-to-end
145 attachment of curcumin particles (Thorat & Dalvi, 2014). This end-to-end attachment creates larger
146 sized aggregates of the curcumin plates. However, with time, the particles appeared to be more fused
147 and such stacks were less visible. Figure 2b presents the SEM image of the curcumin crystals dispersed
148 in dimethyl sulfoxide (DMSO). In DMSO, there appeared to be a shift in aspect ratio to nearly 2:1 to
149 3:1 with appearance of needle-shaped attachments. The appearance of these acicular structures suggests
150 an uncontrolled growth of the curcumin particles from dense non-uniform and highly supersaturated
151 zones in the solution. This uncontrolled nucleation prompted the growth of secondary particles from
152 the main crystal stem (Kurniawansyah, et al., 2017; Thorat & Dalvi, 2014). In presence of edible oils,
153 such as sunflower oil, curcumin crystals with dimensions of 13-23 μm (length) and 3-5 μm (width) were
154 observed (Figure 2c). The particles appeared more fused; possibly caused by a rapid accretion of
155 primary units into single particles, or by particle growth through the process of molecule-by-molecule

156 bonding (Thorat & Dalvi, 2014). However, the exact mechanism of such crystal fusion remains to be
157 uncovered.

158 ## 2.2 Solubility of curcumin in solvents

159 The log P value of curcumin (i.e. the measure of the extent to which a solute preferentially
160 partitions in octanol over the aqueous phase) has been reported to be 3.29 (PubChem-969516). This
161 confirms that the curcumin molecule is highly lipophilic with a low intrinsic water solubility (11 ng/mL,
162 ambient temperature) (Tønnesen, Másson, & Loftsson, 2002). The hydrophobic nature of curcumin is
163 given by an aliphatic chain (bridge), which separates the highly polar enolic and phenolic groups
164 (Balasubramanian, 2006). The bridge is composed of lipophilic methine-rich segments connecting the
165 polar regions of the molecule (Balasubramanian, 2006; Heger, et al., 2014).

166 Curcumin is highly soluble in polar solvents, such as acetone (7.75 mg/ mL), 2-butanone (2.17
167 mg/mL), ethanol (5.6 mg/mL), methanol (4.44 mg/mL), 1,2-dichloroethane (0.5125 mg/mL) and
168 isopropanol (3.93 mg/mL) (Heger, et al., 2014; Khopde, Indira Priyadarsini, Palit, & Mukherjee, 2000).
169 The DMSO is one of the most commonly used solvents for dispersing curcumin as it can dissolve
170 curcumin up to a concentration of ~20 mg/mL, an order of magnitude higher as compared to most
171 alcohols (Khopde, et al., 2000).

172 Authors have reported that in alkaline conditions (> pH 7), curcumin can be dissolved sparsely in
173 water as the acidic phenolic group in curcumin donates its H^+ ion, forming the phenolate ion enabling
174 dissolution (Jagannathan, Abraham, & Poddar, 2012; Tønnesen & Karlsen, 1985). However, under
175 alkaline conditions, curcumin is more susceptible to degradation, partly due to the formation of
176 phenylated anion; this can increase the production of curcumin radicals. These radicals successively
177 mediate degradation of the molecule by reacting with other curcumin radicals to form dimeric
178 catabolites, or by reacting with biomolecules in the cells (Heger, et al., 2014). For in vitro and in vivo
179 studies, curcumin as a free molecule is commonly dissolved in the least toxic-miscible solvents
180 according to their lethal 50% dose values (Heger, et al., 2014). Curcumin is also soluble in different
181 edible oils (Table 1) and such solubility depends on the degree of mixing, temperature-time conditions,
182 which is discussed in detail in Section 5.

183

3 Key challenges of delivery of curcumin

A strong scientific consensus exists that orally administrated curcumin has poor bioavailability due to the poor solubility and limited absorption from the gut of the latter. The bioavailability of curcumin is determined by its bioaccessibility; latter defined as the fraction of the quantity of bioactive initially ingested that is solubilized within the gastrointestinal fluid, in a form that can be absorbed by the epithelium cells (Fernández-García, Carvajal-Lérida, & Pérez-Gálvez, 2009). Since early 1980's, substantial research has been conducted with respect to curcumin bioavailability in rat models. Ravindranath & Chandrasekhara (1980) reported that after oral administration of 400 mg of curcumin in rats, only a trace amount (less than 5 µg/mL) of curcumin remained in the portal blood during 15 min to 24 hours. More recently, Sharma, et al. (2004) found that after an oral dose of 3.6 g of curcumin, maximum curcumin level in plasma was 11.1 nmol/L after an hour of dosing. However, no curcumin was found in plasma from patients who received a lower dose of curcumin. It has been identified that, in rat plasma, glucuronide and sulfate are the major products of curcumin biotransformation (Sharma, et al., 2001). Enzymatic hydrolysis of curcumin through glucuronidase and sulfatase may explain its efficient metabolism and its poor bioavailability when administered orally (Cheng, et al., 2001; Sharma, et al., 2001).

According to the Nutraceutical Bioavailability Classification Scheme (NuBACS), curcumin is classified as $B^*(-)_{L,S}\ A^*(+)\ T^*(-)_{C,M}$. The full classification scheme has been discussed in detail elsewhere (Zhang & McClements, 2016; Zou, et al., 2015b). Briefly, this suggests that the poor degree and rate of release of curcumin from the food structure (L) and the poor solubility in the gastrointestinal fluids (S) are the key factors (−) limiting the bioaccessibility (B*) of curcumin. Furthermore, curcumin absorption (A*) has no major influence on the bioavailability of curcumin. However, the chemical (C) or metabolic (M) degradation of curcumin during its gastrointestinal passage remains as the key limiting factor (-) on the transformation (T*) of curcumin. Hence, it is important to understand how emulsion-based delivery systems can be designed to address these specific challenges. In this review, we have only focused on bioaccessibility, which has yielded most of the publications in the last decade.

4 Emulsion-based delivery systems

Considering the high hydrophobicity of curcumin and our physiology being largely an aqueous-based system, an oil-in-water (O/W) emulsion-based approach has been the most obvious choice to deliver curcumin. In the last decade, a wide range of curcumin-encapsulated emulsion-based systems (Figure 3), such as conventional emulsions stabilized by surfactants, monolayers or multilayers of biopolymers (proteins, polysaccarides), nanoemulsions and Pickering emulsions, have been designed to deliver curcumin (Tables 2 and 3).

In order to set the scene in terms of encapsulation efficiency, protection, retention, stability and release of curcumin, we have included an overview of emulsion-based delivery vehicles, focussing on the design principles, formation and stability of emulsions in the next section..

4.1 Stability of O/W emulsions

An emulsion consists of small droplets of one liquid dispersed in another immiscible liquid. Typically, these two immiscible liquids are oil and an aqueous phase (McClements, 2015; Sarkar & Singh, 2016). Depending on their arrangement, they are usually classified as oil-in-water (O/W) or water-in-oil (W/O) emulsions. Emulsions are thermodynamically unstable systems due to the large interfacial area between the two immiscible phases. Emulsions can destabilize over time due to their thermodynamic instability, causing creaming, sedimentation, flocculation and coalescence of the systems (Dickinson, 2009; McClements, 2015). Creaming and sedimentation are main forms of gravitational separation. When two or more droplets come together and aggregate, but retain their individual integrity, droplets are said to flocculate. Such flocculation might occur due to electrostatic attraction (bridging) or osmotic pressure effects (depletion). When two or more droplets merge together to form a single large droplet, droplets are said to coalesce. “Oiling-off” occurs when excessive droplet coalescence happens and a separate layer of oil is formed on top of the aqueous phase

4.2 Types of emulsion structure

Conventional emulsions. Conventional emulsions have mean droplet radii in the range of 0.2- 100 μm (Figure 3a). They are thermodynamically unstable systems and tend to be optically turbid or opaque as they scatter light because of the droplet dimension being similar to the wavelength of light. The droplet size is mainly determined by the oil phase, as the thickness of the interfacial layer ($\delta \approx$1-15 nm) is much smaller than the radius (r) of the oil droplet core ($\delta << r$). The interfacial layer is generally made up of surfactants (e.g. tweens (polyethoxylated sorbitan esters or polysorbates), spans (sorbitan esters), polyoxyethylene (20) sorbitan monolaurate, monooleate and monopalmitate) or monolayers of biopolymers (e.g. milk proteins (caseins, whey proteins), plant proteins (pea protein, soy protein), and polysaccharides, such as gum Arabic). The preparation method for the formation of conventional emulsions involves using a high shear mixer or two-stage valve homogenizer to homogenize the two immisible phases, as illustrated schematically in Figure 3d.

Multilayered emulsions. A multilayered emulsion consist of emulsion droplets electrostatically stabilized by layers of alternatively charged emulsifiers (Figure 3b). In recent years, there has been growing interest in the utilization of the layer-by-layer (LbL) electrostatic deposition method to form such multilayer emulsion structures. In this method, a charged polyelectrolyte is absorbed through electrostatic attraction onto an oppositely charged droplet surface. Multiple layers can be formed by alternating adsorption of oppositely charged polyelectrolytes or charged emulsifiers leading to the formation of a multilayered structure at the interface (Figure 3e) (Dickinson, 2009; McClements, 2015).

Protein-polysaccharide conjugate-stabilized emulsions. Proteins and polysaccharides possess different inherent characteristics (Goh, Sarkar, & Singh, 2008, 2014). Proteins are known to adsorb at oil/water interface due to their surface-active properties, and polysaccharides are known for their water-binding, gelling and thickening properties. Covalently linked proteins and polysaccharides via maillard reaction between the amino groups of protein and reducing sugar groups of the polysaccharide are used to combine and improve their individual characters and stabilize oil-in-water emulsion with better kinetic stability (Akhtar & Ding, 2017).

Pickering emulsion. Pickering emulsions are stabilized by solid particles that are irreversibly adsorbed to the oil-water interface (Figure 3a) (Aveyard, Binks, & Clint, 2003; Dickinson, 2012, 2017;

Pickering, 1907; Ramsden, 1903). These particles at the interface should have an average size at least 10-100 times smaller than the emulsion droplet size in order to achieve effective Pickering stabilization. The stabilization mechanism for a Pickering emulsion is different from that of a conventional emulsion. In a conventional emulsion, the interfacial materials (e.g. surfactants, biopolymers) with amphiphilic properties impart kinetic stability to the droplets by decreasing the interfacial tension and by generating electrostatic repulsion/ steric hindrance between the droplets.

When compared to conventional emulsions, the irreversible absorption of particles creates a mechanical (steric) barrier in Pickering emulsions that adds long-term physical stability against coalescence and Ostwald ripening. Solid particles in Pickering emulsion present a partial wettability by both the oil and water phase. Depending on their degree of wettability in either of the phases and location at the interface defined by the contact angle of the particle (θ), they can either stabilize O/W or W/O emulsions (Dickinson, 2009, 2012, 2017). If the contact angle is smaller than 90^o ($\theta < 90^o$), the particle will be preferentially wetted by the aqueous phase, favouring the formation of an O/W emulsion. Pickering emulsions can be prepared in a similar way to that of conventional emulsions (Figure 3d).

Depending on the size of the particles, oil droplets of <10 µm diameter can be achieved. However, in most case, food-grade Pickering emulsions prepared using starch and protein-based microgel particles have a considerably higher droplet size (>10 µm), as the particles used to stabilize these droplets are generally sub-micron to micron-sized (Sarkar, et al., 2016a; Yusoff & Murray, 2011). The concept of Pickering emulsion has been present in different food products since long, such as homogenized and reconstituted milk (oil-in-water (O/W) emulsions stabilized by casein micelles) (Dickinson, 2012), it is only recently that there has been an upsurge of research interests to understand the interfacial properties of particles in O/W emulsions. This is largely due to the laboratory-manufactured food-grade particles of controlled size being available now, e.g. whey protein microgel, pea protein microgel, starch, zein, flavonoids etc (de Folter, van Ruijven, & Velikov, 2012; Luo, et al., 2012; Sarkar, et al., 2016a; Shao & Tang, 2016; Yusoff & Murray, 2011).

290 **Nanoemulsions.** Nanoemulsions have a mean radii between 50 and 200 nm (Figure 4a). They
291 tend to be transparent or slightly opaque, and have much better stability to aggregation as compared to
292 that of conventional emulsions due to their very small droplet size. The overall droplet composition is
293 mainly constituted by the emulsifier layer as the thickness of the emulsifier layer is similar to that of
294 the radius of the oil droplet (δ = r) (McClements & Rao, 2011). Fabrication methods for nanoemulsions
295 are typically categorized as either high-intensity or low-intensity and consist of two stages: the pre-
296 emulsification and emulsification stage. High-intensity methods include use of a high-speed blender,
297 high-pressure valve homogenizers, microfluidizers and ultrasonic bath or sonicator (Figure 4b)
298 (McClements & Rao, 2011). These mechanical devices are capable of creating intense disruptive forces
299 that break up the oil phase into small droplets. The low-intensity methods include phase inversion and
300 solvent mixing methods (Figure 4c) (Borrin, Georges, Moraes, & Pinho, 2016). In these methods, the
301 spontaneous formation of tiny oil droplets within the mixed oil–water–emulsifier systems are formed,
302 when the environmental conditions are altered.

303

304 # 5 Dispersion of curcumin into the oil phase

305 Proper dispersion of bioactive compounds into the carrier phase is a key factor for improving the
306 solubility, dissolution behavior, and administration orally (Zhang & McClements, 2016). Curcumin is
307 crystalline at ambient temperature and must therefore be dispersed in a suitable carrier before it can be
308 incorporated into a colloidal delivery system. In an oil-in-water emulsion, the lipid acts as the carrier
309 phase for lipophilic bioactive components. Table 1 summarizes the solubility values (non-exhaustive)
310 of curcumin dispersed in different types of edible oils. The dispersion ability of oil is commonly
311 referred to in the literature, as the ‘loading capacity’ or ‘loading percentage’. The numerical value of
312 the loading capacity is obtained by calculating the quantity of curcumin dispersed in the oil as a
313 percentage of the total quantity of curcumin added. The loading capacity of an oil can vary depending
314 on the molecular weight and polarity of the carrier oil, as well as the physical conditions applied, such
315 as temperature and times used either in the dispersion or in the incubation process.

316 **Molecular weight and polarity of the carrier oil.** Direct experimental evidence suggests that
317 quantity of curcumin that can be solubilized in a carrier oil is inversely proprtional to the average
318 molecular weight of the latter (Ahmed, Li, McClements, & Xiao, 2012). For instance, short chain
319 triglycerides (SCT) have more polar groups (oxygens) per unit mass than long chain triglycerides
320 (LCT). Hence, SCT present more dipole–dipole interactions between their polar groups and the
321 curcumin molecules, thereby favoring curcumin solubilization. Also, greater solubilisation is achieved
322 in SCT compared to LCT due to an excluded volume effect. When curcumin molecules are incorporated
323 into the oil phase, a depletion zone is formed around curcumin molecules. In this region, the center of
324 the lipid molecules is excluded, in other words, the lipid concentration is zero. The thickness of the
325 depletion zone increases with increasing molecular weight of the lipid molecules (Ahmed, et al., 2012).
326 For example, Joung, et al. (2016) reported that the solubility of curcumin in MCT oil was higher when
327 compared to coconut oil (LCT:MCT), olive oil (LCT) and corn oil (LCT) (0.25, 0.1, 0.08, 0.07 mg/mL,
328 respectively) (Table 1). These results were also consistent with a recent study by Ma, et al. (2017a),
329 who reported that solubility of curcumin in MCT was nearly three times as much as canola oil, and
330 twice as much as in lineseed oil, corn oil and sunflower oil (12.4, 4, 7, 6.2 and 5.4 mg/mL , respectively).
331 **Temperature dependence.** Solubility of curcumin is highly temperature-dependent. When a
332 crystalline material is fully dissolved, it is said that the material has reached an equilibrium, but above
333 this level, it will form crystals (supersaturation) (McClements, 2012a). From a theoretical perspective,
334 increasing the temperature increases the average kinetic energy of both, the solution and the crystalline
335 molecules. This increase in kinetic energy destabilizes the solid state of the solute (less able to hold
336 together) and allows the solvent to break apart the solute molecules more effectively and dissolving it
337 more rapidly.
338 To characterize the temperature dependence of the dissolution of crystalline curcumin in oil, the
339 common method used is to determine the reduction in magnitude of turbidity of the oil using a UV-Vis
340 spectrophotometer. For instance, Zou, Liu, Liu, Xiao, & McClements (2015a) observed that the
341 turbidity of curcumin in corn oil mixtures (LCT) decreased appreciably upon heating from 25 to 100
342 ^{o}C. At a concentration of 3 mg/mL, the turbidity almost reached a value close to zero at 100 ^{o}C
343 indicating that the crystals were fully dissolved at this temperature (Table 3-1). Interestingly, upon

cooling, turbidity of the oil was low indicating that the curcumin still remained dissolved within the oil. This might be attributed to either curcumin being below its saturation temperature even at 25 °C, or the curcumin concentration did not exceed the supersaturation level to form curcumin crystals (McClements, 2012a). At 4 mg/mL, the turbidity also decreased as the temperature was increased. Nonetheless, the final turbidity at 100 °C was considerably greater than that observed for the sample containing 3 mg/mL curcumin, which implies that excess curcumin crystals had not dissolved completely. When samples were cooled, the turbidity remained high and even increased slightly, which further highlights that the solubility of curcumin decreased with decreasing temperature, as well as the amount of curcumin present was above the saturation level.

Similarly, Ma, et al. (2017b) observed increased curcumin concentrations in MCT oil when using a boiling bath for 3 min as compared to that of ultrasonic (390 W, one second interval for 30 min) and microwave treatments (780 W, 30 sec). Also, Abbas, Bashari, Akhtar, Li, & Zhang (2014) reported that a curcumin concentration of $\leq$ 6 mg/mL was successfully dissolved in MCT oil at 100 °C, without a noticeable sedimentation during one month storage period when incorporated into a nanoemulsion. However, prolonged heat exposure during solubilization of curcumin in the oil phase can cause decomposition of curcumin. In fact, Wang, Liu, Xu, Yin, & Yao (2016) reported 10% of curcumin decomposition after a heat treatment at 90 °C for 1 hour in the dark.

Time dependence. Dissolution rate of curcumin depends on the nature of the crystals (e.g. surface area, crystallinity, morphology, structure), the nature of the solvent (e.g. polarity), and the physical conditions applied (e.g. stirring speed, temperature and sonication) (McClements, 2012a) (Table 1). Soluble curcumin concentration values varied significantly for soybean oil when mixed for 48 h (ambient temperature) (7380 µg/mL) (Setthacheewakul, Mahattanadul, Phadoongsombut, Pichayakorn, & Wiwattanapatapee, 2010) as compared to that for 10 min (0.1834 µg/mL) (Lin, Lin, Chen, Yu, & Lee, 2009). In MCT oil, a soluble curcumin concentration range of 7.50 - 250 µg/mL has been reported when mixed at 60 °C for 10 min, with subsequent 20 min of sonication (Ahmed, et al., 2012; Joung, et al., 2016). Overal, the results suggest that solubility of curcumin depends on the nature of the oil, the curcumin-oil interactions, and the processing conditions (temperature, agitation time); such factors are critical for the maximum incorporation of curcumin into the oil phase. Various studies

have shown that a higher curcumin concentration is generally favored by MCT oil when high temperatures (≥ 60 °C) and appropriate agitation times (10 - 30 min) are applied.

6 Physicochemical stability of curcumin–loaded emulsion systems

Tables 2 and 3 summarize a non-exhaustive list of the emulsion-based approaches used for delivering curcumin, such as nanoemulsions and macroemulsions stabilized by surfactants, protein-polysaccharide conjugates, and Pickering paticles respectively. In this Section, we reviewed various factors that can influence the retention capacity of curcumin, the effect of curcumin incorporation on the droplet size distribution of emulsions and the structural characteristics that promote retention of curcumin during storage and in vitro release.

6.1 Loading efficiency

In literature, the terms, such as "yield", "encapsulation efficiency", "incorporation efficiency" and "loading efficiency" have often been used interchangeably for emulsion-based encapsulation systems. In each case, it essentially refers to the entrapment capacity of an emulsion system. Quantitative information is obtained by measuring the mass of curcumin entrapped into the delivery system as a percentage of the total curcumin added (McClements, Decker, Park, & Weiss, 2009). Since curcumin is required in high concentrations to show therapeutic benefits, one of the prerequisites in the delivery research is high entrapment of bioactive molecules. The loading efficiency of emulsions is highly dependent on the type of emulsifier and its structural arrangements at the interface.

Curcumin-surfactant interactions. Curcumin molecules contain mainly hydrophobic but also some hydrophilic groups that can directly interact with surfactant molecules mainly via hydrophobic and electrostatic interaction, respectively (Yu & Huang, 2010). It has been reported that the enolic and phenolic groups of curcumin underwent electrostatic interactions with positively charged head group of cationic-nonionic surfactant micelles mixtures (e.g. Dodecylethyldimethylammonium bromide (DDAB), Polyoxyethylene 10 oleyl ether, Tyloxapol, Polysorbate 80), while the methylene rich chain of curcumin interacted with the hydrophobic part of the surfactant micelles mixture (Kumar, Kaur,

399 Kansal, Chaudhary, & Mehta, 2016). The authors revealed using transmission electron microscopy
400 (TEM) that curcumin was not located within the core of the surfactant micelles, but was rather
401 interacting with the polar part of the surfactants (head group). This suggests that in emulsions stabilized
402 by mixed surfactant systems, both hydrophilic and hydrophobic parts of the surfactants might contribute
403 to the solubilisation of curcumin. Such favorable microenvironment mediated by the surfactant systems
404 might enable enhancing the solubilisation of curcumin molecules inside the emulsions leading to a high
405 loading efficiency. For example, when 15 mg of curcumin was added in nanoemulsions stabilized by
406 optimized mixtures of hydrogenated L-α-phosphatidylcholine (HEPC) (surfactant) and
407 Polyoxyethylene hydrogenated castor oil 60 (HCO-60) (co-surfactant) or HEPC and Tween 80, loading
408 efficiencies of 100% or ~97%, respectively, were obtained (Anuchapreeda, Fukumori, Okonogi, &
409 Ichikawa, 2012a).

410 **Curcumin-protein interactions.** Sodium caseinate, a mixture of α_{s1}-, α_{s2}- and β- caseins and κ-
411 casein is commonly used to stabilize oil droplets (Sarkar & Singh, 2016). The α_{s1}-, α_{s2}- and β- caseins
412 are phosphoproteins and are more hydrophobic than κ-casein. This is because α_{s1}-casein contains two
413 tryptophan residues at positions 164 and 199, whereas κ-casein has one tryptophan residue at position
414 143 (Liu & Guo, 2008). It is highly likely that when sodium caseinate-stabilized emulsions are used to
415 encapsulate curcumin, any or all of these tryptophan (hydrophobic) residues directed towards the oil
416 phase could bind to curcumin molecules through hydrophobic interactions and contribute to increasing
417 the loading efficiency of an emulsion (Pan, Zhong, & Baek, 2013). For example, Rao & Khanum (2016)
418 observed a considerable increase in the loading efficiency when the sodium caseinate concentration was
419 increased from 2.5% (89.6%) to 10% (92.3%) in nanoemulsions at a constant curcumin-milk fat ratio
420 of 1:0.05% (w/w) (Table 2).

421 **Curcumin-polysaccharides interactions.** Curcumin-polysaccharide interactions can also affect
422 the loading efficiency. Recently, Li, Hwang, Chen, & Park (2016) have investigated the influence of
423 chitosan multilayer on the physicochemical properties of curcumin-loaded nanoemulsions. The loading
424 efficiency was found to be 95.1% when a curcumin concentration of 0.548 mg/mL was used. This was
425 presumably due to the interactions between keto groups of curcumin in either the diketo or the cis–enol
426 form, and the amine groups of chitosan (Anitha, et al., 2011). Chitosan, which is rich in protonated

amino groups possibly facilitated the electrostatic interaction between the cationic groups located on the polyglucosamine chains of the molecule and the negatively charged anionic curcumin. In addition, at physiological pH (7.4) conditions, the hydrophobic interactions of curcumin with chitosan was reported to be more pronounced in the presence of nonionic surfactant (Tween 80) than in the presence of cationic surfactants, such as, cetyl trimethyl ammonium bromide (CTAB). In Tween 80 systems, the binding process was hypothesized to be driven by hydrophobic, electrostatic and hydrogen bond formation between curcumin and chitosan (Boruah, Saikia, & Dutta, 2012).

Interfacial structure. The development of a protein-polysaccharide conjugate has been reported to act as a physical barrier that prevents the diffusion of loaded curcumin into the aqueous phase (Qi, Huang, He, & Yao, 2013; Wang, et al., 2016). Often, one or more co-solvents or surfactants are added to the formulation to assist the solubilisation of high concentrations of curcumin in the system. For example, Wang, et al. (2016) investigated protein-polysaccharide conjugates-stabilized emulsions that are suitable for delivery of curcumin (Table 3). They used a combination of MCT oil with a co-solvent ethanol (90:10 (v/v) to prepared bovine serum albumin and dextran conjugate (BSA-dextran)-stabilized emulsion, the conjugate was formed between the e-amino group in BSA and the reducing-end carbonyl group in the dextran. It was observed that the conjugates form a BSA film at the oil/water interface with the dextran shell, the latter acted as a steric barrier retaining the loaded curcumin by preventing its diffusion into the aqueous phase, latter would have been facilitated by the carrier-acting ethanol otherwise. At BSA concentration of 15 mg/mL in the aqueous phase, the curcumin loading efficiency was higher than 99% (Qi, et al., 2013; Wang, et al., 2016). Xu, Wang, & Yao (2017) used a similar oil mixture (90% MCT and 10% ethanol (v/v)) and observed similar behaviour for casein-soy soluble polysaccharide (CN/SSPS) conjugate-stabilized emulsions at pH 3-4.5, at this pH the protein and the polysaccharide carried opposite charges forming a rather integrated interfacial film via electrostatic interactions (Table 3). About 99.9% of curcumin was encapsulated in the droplets (Xu, et al., 2017).

Irreversible adsorption of individual particles in Pickering emulsion forms a porous interfacial layer (pores referring to space between the stabilizing particles at the interface) that may reduce the curcumin content by facilitating the diffusion of oxidation initiators into the oil droplets, latter may promote oxidative degradation/ modification or alkalyne hydrolysis of curcumin (Tønnesen, Karlsen,

455 & van Henegouwen, 1986; Tønnesen, et al., 2002). Previously, it has been estimated that the gaps
456 between particles in a whey protein microgel-stabilized emulsion is ~110 nm for microgel particles of
457 size d_0 = 300 nm (Sarkar, et al., 2016a). However, such gap dimension can effectively be controlled by
458 fusing the particles together forming a discrete layer or using smaller-sized particles. This was
459 successfully shown in emulsions stabilized by smaller-sized kafirin particles (size range of 92–434 nm),
460 where a loading efficiency of ~90% was achieved because of the reduced gap dimension, latter limited
461 the degradation of curcumin (Table 3). In another study, emulsions stabilized by non-heated (NHT)
462 octenyl succinate (OSA) modified quinoa starch granules (2 µm) had a relatively low loading efficiency
463 of curcumin (~ 80%) due to potential diffusion of oxidation initiators through the larger gaps in between
464 the particles (Marefati, Bertrand, Sjöö, Dejmek, & Rayner, 2017; Xiao, Li, & Huang, 2015; Xiao,
465 Wang, Gonzalez, & Huang, 2016) (Table 3). Interestingly, a thermal treatment of OSA modified starch
466 granule-stabilized emulsions had created a rather fused layer of partially gelatinized starch granules,
467 reducing the gaps between particles and favouring a higher protection of curcumin in undegraded form
468 within the system.
469

470 ## 6.2 Droplet size of curcumin-loaded emulsions

471 In theory, incorporation of curcumin should not alter the droplet size of a system if emulsion
472 droplets are in the order of few microns (McClements & Li, 2010). Curcumin crystal size and emulsifier
473 concentration can influence the extent of increase of droplet size after curcumin incorporation,
474 particularly relevant in the case of nanoemulsions.

475 **Curcumin crystal size.** Nanoemulsion droplets usually have a mean diameter between 50 and
476 200 nm. Hence, it is highly likely that under specific dispersion conditions (e.g. temperature), curcumin
477 crystal growth could interfere with the droplet size of the nanoemulsions. This clearly limits the amount
478 of curcumin that can be successfully incorporated within the nanoemulsion droplets, since the concentration
479 should always remain below the saturation limit (McClements & Rao, 2011). For instance,
480 incorporation of curcumin into surfactant-stabilized nanoemulsions has been reported to increase the
481 average droplet size of the emulsion, thereby destabilizing the system. Borrin, et al. (2016) observed
482 that encapsulating 0.1% curcumin into nanoemulsion stabilized by Tween 80 caused a statistically

significant increase in the hydrodynamic diameter from 200 to 270 nm, after 60 days of storage. However, the increase was not observed in nanoemulsions containing less curcumin (0.03-0.07%). (Table 2). Similar findings were reported by Anuchapreeda, et al. (2012a) where increasing the amount of curcumin from 15 to 240 mg increased the mean hydrodynamic diameter of nanoemulsion from 48 to 78 nm.

On the contrary, in coventional emulsions and emulsions stabilized by protein-polysachharide complex as well as edible Pickering particle-stabilized emulsions (Table 3), the size of curcumin crystals remains comparatively smaller (10 - 1000 times) as compared to that of the emulsion droplets. Hence, in these systems no significant change in the emulsion droplet size distribution occurs after curcumin encapsulation (Marefati, et al., 2017; Shah, et al., 2016a; Wang, et al., 2016; Xu, et al., 2017). Thus, changes in the droplet size after curcumin incorporation is mainly a phenomenon in nanometer-sized emulsions. Bioactive components are required in high concentrations to show therapeutic benefits; therefore, the quantity of curcumin that can be incorporated into nanoemulsions without altering the droplet size can be a potential limiting factor. Furthermore, protein-polysaccharide conjugates/complexes, Pickering emulsion systems with a larger droplet size appear to be rather less sensitive to such alteration in droplet size after curcumin incorporation.

7 In vitro gastrointestinal stability and bioaccessibility of curcumin-loaded emulsions

An important parameter for characterizing the effectiveness of a delivery system is the protection of the encapsulated material until it reaches the targeted location. For curcumin, oxidative degradation/ modification that are mediated by reactive oxygen species (ROS), such as, hydroxyl radical (•OH), superoxide anion ($O_2^{\bullet -}$), peroxyl radicals and alkaline hydrolysis are the two major challenges encountered in in vitro stability studies that hinder the use of curcumin as a pharmaceutical (Wang, et al., 1997). The most common pharmaceutical approach to assess in vitro degradation and release of curcumin from emulsion based systems involves addition of a buffer solution at different pH, or phosphate buffer containing cosolvents, such as, ethanol/methanol, salts (e.g. $CaCl_2$) and in some cases

bile salts in a dialysis bag (e.g. 3,500-8,000 Da) subjected to mechanical forces (e.g. shaking, stirring) at temperature in the range of 22-37 ^{o}C. In these pharmaceutical approaches, the degradation of curcumin under various pH conditions are investigated. In other cases, release of curcumin is facilitated by the use of polar solvents mixed with the buffer solution, here, the quantity of curcumin released from the emulsion to the buffer containing ethanol/ methanol is generally expressed as the percentage of the original curcumin encapsulated within the emulsion systems. However, for in vitro digestion models used by food scientists, this "release" term can be misleading as no such cosolvents are employed. In these studies, curcumin can only be released from an emulsion as part of an oil phase i.e. within the free fatty acids (FFAs), mono and/or diacylglycerols released during lipid digestion in the intestinal phase. Since pH change is a crucial parameter in in vitro gastrointestinal models and curcumin degradation is highly dependent on pH conditions, in vitro digestion results can be better interpreted in terms of degradation of curcumin rather than release, latter is only relevant when discussing the curcumin release along with the lipid digestion products as indicated above.

7.1 In vitro storage stability and release

Encapsulation of curcumin in Pickering emulsions have shown to significantly improve the storage stability of curcumin. For example, Tikekar, Pan, & Nitin (2013) assessed the storage stability comparing the rate of curcumin degradation between curcumin solubilized in a buffer solution (3% (v/v) methanol) at pH 5.7, and curcumin encapsulated in silica-stabilized Pickering emulsions at pH 6.5. When incorporated into a Pickering emulsion system the time required for 50% reduction in curcumin concentration (half-life) was approximately 87 hours, compared to 50 minutes observed for free curcumin (Table 3). Considering that the stability of curcumin decreases in buffered systems at neutral to alkaline pH conditions (Wang, et al., 1997), these results show that encapsulation of curcumin in Pickering emulsion significantly improved the storage stability of curcumin.

Unfortunately, the non-biodegradable and non-digestible character of silica has limited its application as delivery systems; increasing the interest in food-based particles, such as protein-based, and carbohydrate-based particles as Pickering emulsion stabilizers (Sarkar, et al., 2016a; Yusoff & Murray, 2011). Chitosan-tripolyphosphate nanoparticles (CS-TPP-NPs) have been recently used due to

its non-toxic (solvent free) and easy formation technique through ionic gelation process (Table 3). The CS-TPP nanoparticles were formed by cross-linking the primary positively charged amino groups of CS with the polyanion TPP, which is negatively charged. Shah, et al. (2016a) observed that the curcumin degradation was ~14 wt% after 24 hours storage in the dark (22°C) for CS-TPP-NPs emulsions prepared with 5 and 20 wt% MCT oil. The half-life (50 wt%) of curcumin was more than 120 hours.

Additionally, during an in vitro release model consisting of phosphate buffer containing ethanol (15% v/v) at acidic conditions (pH 2), which relates to gastric conditions, the release of curcumin from CS-TPP-stabilized Pickering emulsion after 24 and 96 hours was 56% and 82%, respectively. In almost neutral conditions (pH 7.4), which relates to blood fluid, 37% and 74% of curcumin was released within the same time interval. This lower curcumin retention, under acidic conditions, was also reported by Kakkar, Singh, Singla, & Kaur (2011) for curcumin-loaded solid lipid nanoparticles, and attributed to the increase of solubility of curcuminoids under acidic conditions previously discussed in section 2.1. Compared to silica-stabilized Pickering emulsions, curcumin storage stability was higher in Pickering emulsions stabilised with CS-TPP-NPs (Table 3).

7.2 In vitro gastrointestinal stability of curcumin

In vitro digestion models are commonly used to study the stability and digestibility of encapsulated bioactive compounds in different parts of the gastrointestinal tract (GIT) (Laguna, Picouet, Guàrdia, Renard, & Sarkar, 2017; Minekus, et al., 2014; Sarkar, Goh, & Singh, 2010a; Sarkar, Goh, Singh, & Singh, 2009b; Sarkar, Horne, & Singh, 2010b, 2010c; Sarkar, et al., 2016a; Sarkar, Ye, & Singh, 2016b; Singh & Sarkar, 2011). Simulated gastric fluids (SGF) involve the addition of salts (e.g. NaCl), acids (e.g. HCl) and digestive enzymes (e.g. pepsin) at a highly acidic pH value (e.g. 1.2- 4) for a fixed period of time (e.g. 2 hours) at a body temperature of 37 ^{o}C. Simulated intestinal fluids (SIF) involve the addition of bile salts (or bile extract), pancreatin (trypsin, amylase, lipase) and salts (e.g. $CaCl_2$, NaCl, KH_2PO_4), at around neutral to alkaline pH values (e.g. 6.5–7.5) for a fixed period of time (e.g. 2- 3 hours) at a body temperature of 37 ^{o}C. In some digestion models, an initial oral stage is also included,

564 which contains salts, glycoporoteins (e.g. mucin) and α-amylase, around a neutral pH value for a fixed
565 period of time (e.g. 5- 10 min.) at a body temperature of 37 ^{o}C (Sarkar, Goh, & Singh, 2009a; Sarkar &
566 Singh, 2012; Sarkar, Ye, & Singh, 2017a).

567 **Proteolysis and/or displacement of interfacial materials.** The structural conformations of
568 proteins determines the ability of pepsin to hydrolyse the proteins. Native β-lactoglobulin has been
569 reported to be resistant to pepsin breakdown in simulated gastric digestion due to its compact globular
570 structure (Fu, Abbott, & Hatzos, 2002; Sarkar, et al., 2010a; Sarkar, et al., 2009b; Scanff, et al., 1990;
571 Singh & Sarkar, 2011). However, when present at the interface, it can be hydrolysed by gastric and
572 pancreatic enzymes (Sarkar, et al., 2009b; Sarkar, Zhang, Murray, Russell, & Boxal, 2017b). This is
573 particularly important for protein-based particle stabilized interfaces, such as whey protein microgel,
574 kafirin and bovine serum albumin. Kafirin's structure comprises of an α-helix and β-sheet secondary
575 structure, and exhibits extensive disulphide-induced cross-linking (Belton, Delgadillo, Halford, &
576 Shewry, 2006). Xiao, Wang, Perez Gonzalez, & Huang (2016) observed that under gastric digestion,
577 without the addition of pepsin, curcumin loaded kafirin-stabilised Pickering emulsions (KPE) suffered
578 less droplet coalescence after 30 min of digestion as compared to that in the presence of pepsin (Table
579 3). With the addition of pepsin to the SGF, KPE showed coalescence with the apperance of larger
580 droplets within 30 min. At the end of the gastric treatment (1 hour), the majority of the oil droplets lost
581 their integrity and macro-scale phase separation occurred.

582 Protein-stabilized interfaces are highly responsive to intestinal conditions. Bile salt, a bio-surfactant
583 in intestinal fluids can competitively displace the β-lactoglobulin protein from the droplet interface
584 (Sarkar, et al., 2010b; Sarkar, et al., 2016a; Sarkar, et al., 2016b), thereby favouring lipase activity and
585 degradation of curcumin through exposure to ROS such as hydroxyl radical. For example, Sari, et al.
586 (2015) reported that curcumin nanoemulsions, stabilized by whey protein concentrate (WPC) and
587 composed of 50-60% β-lactoglobulin, were stable to gastric digestion (2 hours) with 90% of the
588 encapsulated curcumin stable in the nanoemulsion (Table 2). However, during intestinal digestion 77%
589 of the curcumin was degraded, attributed to the destabilization of the emulsions after 2 hours of
590 incubation in the intestinal phase.

591 **Barrier properties of interfacial materials.** When treated under specific thermal conditions,

Pickering particle-based interface can provide a certain degree of barrier to the access of bile salts or lipase to the oil-water interface. For example, in case of Pickering emulsions stabilized by gelatinised starch (Marefati, et al., 2017) or whey protein microgel (Sarkar, et al., 2016a), a thermal treatment was necessary for the formation of a fused barrier layer of connected particles at the interface (as discussed in Section 6) and might restrict the penetration of bile salts and/or enzymes. For example, Marefati, et al. (2017) reported higher curcumin stability after 60 min of oral (~95%) and 2 hours of intestinal (~86%) digestion for heated Pickering-stabilized emulsions (HT) stabilized with OSA-treated quinoa starch granules, as compared to that of the non-heated samples (NHT) (~70% and ~40%, respectively) (Figure 3). However, no statistically significant difference between these samples was seen after 120 min of gastric digestion (Table 5a) (~82% for HT and ~86% NHT). This suggests that a fused layer of starch granules was significantly effective as a barrier layer against amylase attack (oral and intestinal regimes) as compared to that of intact starch granules, by reducing the gap dimensions. A recent study has shown that gastric destabilization of protein stabilized interfaces can be hindered by binding a secondary layer of oppositely charged polysaccharide-based particles, such as cellulose nanocrystals (Sarkar, et al., 2017b). As cellulose nanocrystals are not digested by pepsin and provide a high surface viscosity, they provide a strong barrier to the pepsin attacking the whey protein at the droplet surface (Sarkar, et al., 2017b). However, use of such secondary layer of particles in a proteinaceous particle-stabilized interface and role of such secondary layer of particles at interface in protecting curcumin in the entire gastrointestinal regime is yet to be explored in literature.

Through the implementation of in vitro digestion models, it has been demonstrated that, curcumin degradation is higher during simulated intestinal digestion or neutral pH than in simulated gastric digestion, regardless of the emulsion-based approach. Emulsions stabilized by ionic surfactants, proteins and electrostatically charged protein-polysaccharide multilayered complexes are highly sensitive to any pH and ionic strength alterations, which are essentially abundant in physiology. In in vitro digestion regimes, Pickering particles appear to be more capable to protect curcumin from degradation in emulsions than that of the low molecular weight emulsifiers/ protein owing to the strong adsorption of the particles to the oil-water interface and not being displaced by ‘bio-surfactant’ bile salts (Sarkar, et al., 2016a). The effective formulation of emulsion systems exhibiting a mass transport

barrier to enzyme attack, stability to changes in pH and delayed act of bile salts and lipid-lipase interactions through the establishment of a protective fused interface enclosing the droplet can be an effective strategy to enacapulate curcumin (Marefati, et al., 2017).

7.3 Bioaccessibility of curcumin-loaded emulsions

Oil droplets are composed of digestible lipids such as triacylglycerols and they generate free fatty acids (FFAs) and monoacylglycerols (MAGs) upon digestion. Mixed micelles are formed by the interactions of these FFAs and MAGs that are released from the oil droplets, phospholipids, bile salts, and cholesterol (Devraj, et al., 2013). These mixed micelles have non-polar domains capable of solubilizing hydrophobic bioactive compounds, and certain types of micelles are small enough to transport the bioactives through the mucus layer to the epithelium cells where they are absorbed (Zhang and McClements, 2016). In particular, bioaccessibility of curcumin is influenced by many factors, including oil composition, droplet size and curcumin-emulsifier interactions.

Oil composition. Various studies have revealed that the bioaccessibility of curcumin is clearly dependent on the type and amount of carrier lipid. Ahmed, et al. (2012) observed that the bioaccessibility of curcumin in β-lactoglobulin-stabilized nanoemulsions increased substantially when the carrier lipid was composed of medium-chain triacylglycerols (MCT) or long-chain triacylglycerols (LCT) due to their ability to form mixed micelles (~41% for LCT and ~58% for MCT oil at a lipid concentration of 2 wt%) (Table 3). The authors also reported higher curcumin bioaccessibility values when the total lipid concentration of MCT oil was increased because more mixed micelles were formed to solubilise the curcumin (~8% at 1% lipid concentration and ~58% at 2% lipid concentration). However, for LCT oil, the bioaccessibility was similar with increased lipid content because a greater fraction of lipid phase was not digested, this means that some of the curcumin was not solubilised from the droplets into the surrounding micellar phase (~20% at 1% lipid concentration, ~40% at 1.5% lipid concentration and ~41% at 2% lipid concentration) (Table 3).

Conversely, other authors have reported that micelles are more likely to be formed by LCT than for MCT fatty acids. Medium chain triglycerides form a mixed micellar phase that contains hydrophobic domains that could not be large enough to accommodate large hydrophobic bioactive molecules such

as curcumin (Zou, et al., 2016). For example, Shah, Zhang, Li, & Li (2016b) deliberately prepared chitosan-tripolyphosphate nanoparticle-stabilized Pickering emulsions (PMCT, PLCT) and nanoemulsions stabilized by non-ionic surfactants (Span 80: Tween 80) (NEMCT, NELCT). A significant difference in curcumin bioaccessibility was reported when using MCT and corn oil (LCT) as the carrier lipids (Tables 2 and 3). The bioaccessibility was ~32% for NEMCT; ~65% for NELCT against 21% for PMCT and 53% for PLCT.

Droplet size. Emulsions with a smaller droplet size have higher lipid/water surface area to volume ratio that may result in higher degree of lipolysis (Armand, et al., 1999). Under physiological conditions, lipases are in excess relative to the quantity of oil droplets, hence a larger lipid/water interface will allow the anchoring of more lipase molecules to the oil/water interface (Armand, et al., 1999). For example, Pinheiro, et al. (2013) reported nearly 10-fold increase in curcumin bioaccessibility during sequential digestion (initial, stomach, duodenum, jejunum, ileum) for nanoemulsions stabilized by Tween 20 (e.g. ~15% in ileum) when compared with nanoemulsions stabilized by dodecyltrimethylammonium bromide (DTAB) (e.g. ~1.5% in ileum) (Table 3). This increased bioaccessibility for Tween 20 nanoemulsions correlated well with the reduced size of the emulsion droplet that was present throughout the simulated digestion (~100-310 nm), especially during duodenum, jejunum and ileum phases as compared to that of the size of DTAB nanoemulsions (~80 – 890 nm) (Table 2). Increasing the concentration of surfactants in nanoemulsions can decrease the emulsion droplet size (McClements, 2012b) and consequently the degree of lipid digestion. On the other hand, studies have found that increasing the surfactant concentration can also result in barrier effect that could also hinder the amount of FFA released (Joung, et al., 2016). This suggests that the amount of surfactant concentration in curcumin nanoemulsions affects the FFA release and the size of the emulsion droplets (the lipid/water interfacial area), which is a key physicochemical factor in curcumin bioaccessibility. Other studies comparing the bioaccessibility of curcumin in β-lactoglobulin-stabilized conventional and nanoemulsions observed that the bioaccessibility of curcumin was fairly similar for both samples, with 58% for nanoemulsions, and 59% for conventional emulsions (Ahmed, et al., 2012) (Table 3). Hence, it appears that there is no consensus in findings so far on advantages of using nanoemulsions over conventional emulsions to encapsulate curcumin from bioaccessibility stand point.

Curcumin-emulsifier interactions. Some multilayer-stabilized nanoemulsions studies have shown that curcumin in these systems had relatively low total curcumin bioaccessibility, potentially due to emulsifier-curcumin interactions (Pinheiro, Coimbra, & Vicente, 2016). For example, nanoemulsions stabilized by lactoferrin (L-NE) and lactoferrin/alginate (L/A-NE) multilayer structure have shown relatively low curcumin bioaccessibility of around ~2.5- 3.1% in jejunum and ileum. These results may be explained by the fact that curcumin may have been bound to the lactoferrin molecules or digestion products of lactoferrin after lipid hydrolysis, hence curcumin was not detected in the micellar phase (Tokle, Mao, & McClements, 2013). Similarly, it has been suggested that cationic polymers may electrostatically inhibit lipase and bile salt action during lipolysis in the small intestine, decreasing the bioaccessibility of lipophilic compounds (Kido, et al., 2003). However, experiments with chitosan-coated nanoemulsions stabilized by Tween 80 have suggested that chitosan coating had a very limited effect on the bioaccessibility of curcumin despite the possible interactions between curcumin and the amine groups of chitosan (Li, et al., 2016). Hence, further studies using standardized in vitro digestion protocol is needed to arrive at a clear consensus on the influence of droplet size and emulsifier charge on curcumin bioaccessibility.

8 Conclusions and Future Outlook

Oil-in-water emulsions have been used as delivery systems for encapsulating and orally administering curcumin. The key factors affecting the stability, release, and bioaccessibility of curcumin in various emulsion-based systems are emulsion droplet size, oil composition and volume fraction, dispersion conditions of curcumin in the oil phase/oil type and structure/density/ type of interface and susceptibility of the interface to physiological breakdown. These factors may act either individually or synergistically.

Extensive studies have been performed to optimize and design effective nanoemulsion systems with improved physicochemical stability, release and bioaccessibility. Emulsions with smaller particle size tend to have better kinetic stability than that of conventional emulsions. Nevertheless, higher emulsifier concentrations are needed to produce smaller droplet size and some surfactants are allowed at significantly low levels. Furthermore, the size of the nanoemulsions seems to be altered on

703 incorporation of micron-sized curcumin crystals. There are some evidences that nanoemulsions might
704 result in higher degree of lipid digestion products by virtue of their high interfacial area and thus, form
705 of higher quantities of mixed micelles. However, there is still debate on specific advantage from the
706 bioaccessibility point of view, in using nanoemulsions versus conventional emulsions to encapsulate
707 curcumin, which requires further investigation. Conventional emulsions on the other hand, particularly
708 the ones stabilized by ionic surfactants, biopolymers, protein-polysaccharide complexes suffer from
709 destabilization in the gastrointestinal regime due to their responsiveness to physiological pH, ionic
710 strengths and enzymes. Thus, they cannot protect the curcumin from physiological destabilization and
711 oxidation before the encapsulated curcumin can reach the targeted sites.

712 Literature on Pickering emulsion for encapsulating curcumin is relatively scarce till date due to
713 the very recent availability of laboratory-designed food-grade Pickering stabilizers. Nevertheless, at
714 this early stage, Pickering emulsion shows promises in terms of in vitro gastrointestinal stability and
715 barrier property to bile salts-induced displacement. Although bioaccessibility studies in nanoemulsions
716 have been well documented in literature, very few studies have been conducted to assess the
717 bioaccessibility of curcumin using Pickering emulsion approach. Further research is needed in this area
718 of Pickering emulsions stabilized by intact or fused layer of particles of biodegradable origin to create
719 highly stable emulsion that can be used to deliver curcumin. It will be important to identify innovative
720 design principles for these Pickering emulsions to release the encapsulated curcumin in a controlled
721 manner in targeted sites in human physiology and generate mechanistic insights in mixed micelles
722 formation. Finally, designing emulsion structures loaded with curcumin together with mapping of their
723 physical, chemical and biological fates during physiological lipid digestion (using in vitro, in vivo and
724 clinical trials) is necessary to rationally design future curcumin-rich food, pharmaceuticals and
725 nutraceuticals.

726

727 ## Acknowledgements

728 Author AAC acknowledges support from the Mexican National Council of Science and Technology
729 (CONACyT) for the award of an Academic Scholarship for her Postgraduate Studies. Authors would

like to thank Mr. Martin Fuller from Faculty of Biological Sciences at University of Leeds for assistance with the SEM images that have greatly improved the manuscript.

References

Abbas, S., Bashari, M., Akhtar, W., Li, W. W., & Zhang, X. (2014). Process optimization of ultrasound-assisted curcumin nanoemulsions stabilized by OSA-modified starch. Ultrasonics Sonochemistry, 21, 1265-1274.

Abbas, S., Karangwa, E., Bashari, M., Hayat, K., Hong, X., H. R. Sharif, & Zhang, X. (2015). Fabrication of polymeric nanocapsules from curcumin-loaded nanoemulsion templates by self-assembly. Ultrasonics Sonochemistry, 23, 81-92.

Ahmed, K., Li, Y., McClements, D. J., & Xiao, H. (2012). Nanoemulsion- and emulsion-based delivery systems for curcumin: Encapsulation and release properties. Food Chemistry, 132, 799-807.

Ak, T., & Gülçin, İ. (2008). Antioxidant and radical scavenging properties of curcumin. Chemico-Biological Interactions, 174, 27-37.

Akhtar, M., & Ding, R. (2017). Covalently cross-linked proteins & polysaccharides: Formation, characterisation and potential applications. Current Opinion in Colloid & Interface Science, 28, 31-36.

Anitha, A., Deepagan, V. G., Divya Rani, V. V., Menon, D., Nair, S. V., & Jayakumar, R. (2011). Preparation, characterization, in vitro drug release and biological studies of curcumin loaded dextran sulphate–chitosan nanoparticles. Carbohydrate Polymers, 84, 1158-1164.

Anuchapreeda, S., Fukumori, Y., Okonogi, S., & Ichikawa, H. (2012a). Preparation of Lipid Nanoemulsions Incorporating Curcumin for Cancer Therapy. Journal of Nanotechnology, 2012, 1-11.

Anuchapreeda, S., Fukumori, Y., Okonogi, S., & Ichikawa, H. (2012b). Preparation of lipid nanoemulsions incorporating curcumin for cancer therapy. Journal of Nanotechnology, 2012, 11.

Armand, M., Pasquier, B., André, M., Borel, P., Senft, M., Peyrot, J., Salducci, J., Portugal, H., Jaussan, V., & Lairon, D. (1999). Digestion and absorption of 2 fat emulsions with different droplet sizes in the human digestive tract. The American Journal of Clinical Nutrition, 70, 1096-1106.

Aveyard, R., Binks, B. P., & Clint, J. H. (2003). Emulsions stabilised solely by colloidal particles. Advances in Colloid and Interface Science, 100, 503-546.

Balasubramanian, K. (2006). Molecular orbital basis for yellow curry spice curcumin's prevention of alzheimer's disease. Journal of Agricultural and Food Chemistry, 54, 3512-3520.

Bansal, S. S., Goel, M., Aqil, F., Vadhanam, M. V., & Gupta, R. C. (2011). Advanced drug-delivery systems of curcumin for cancer chemoprevention. Cancer prevention research (Philadelphia, Pa.), 4, 1158-1171.

Belton, P. S., Delgadillo, I., Halford, N. G., & Shewry, P. R. (2006). Kafirin structure and functionality. Journal of Cereal Science, 44, 272-286.

Bisht, S., Feldmann, G., Soni, S., Ravi, R., Karikar, C., Maitra, A., & Maitra, A. (2007). Polymeric nanoparticle-encapsulated curcumin ("nanocurcumin"): a novel strategy for human cancer therapy. Journal of Nanobiotechnology, 5, 3.

Borrin, T. R., Georges, E. L., Moraes, I. C. F., & Pinho, S. C. (2016). Curcumin-loaded nanoemulsions produced by the emulsion inversion point (EIP) method: An evaluation of process parameters and physico-chemical stability. Journal of Food Engineering, 169, 1-9.

Boruah, B., Saikia, P. M., & Dutta, R. K. (2012). Binding and stabilization of curcumin by mixed chitosan–surfactant systems: A spectroscopic study. Journal of Photochemistry and Photobiology A: Chemistry, 245, 18-27.

783 Cheng, A.-L., Hsu, C.-H., Lin, J.-K., Hsu, M.-M., Ho, Y.-F., Shen, T.-S., Ko, J.-Y., Lin, J.-
784 T., Lin, B.-R., & Ming-Shiang, W. (2001). Phase I clinical trial of curcumin, a
785 chemopreventive agent, in patients with high-risk or pre-malignant lesions.
786 Anticancer Res, 21, 2895-2900.
787 Cui, J., Yu, B., Zhao, Y., Zhu, W., Li, H., Lou, H., & Zhai, G. (2009). Enhancement of oral
788 absorption of curcumin by self-microemulsifying drug delivery systems. International
789 Journal of Pharmaceutics, 371, 148-155.
790 de Folter, J. W. J., van Ruijven, M. W. M., & Velikov, K. P. (2012). Oil-in-water Pickering
791 emulsions stabilized by colloidal particles from the water-insoluble protein zein. Soft
792 Matter, 8, 6807-6815.
793 Devraj, R., Williams, H. D., Warren, D. B., Mullertz, A., Porter, C. J. H., & Pouton, C. W.
794 (2013). In vitro digestion testing of lipid-based delivery systems: Calcium ions
795 combine with fatty acids liberated from triglyceride rich lipid solutions to form soaps
796 and reduce the solubilization capacity of colloidal digestion products. International
797 Journal of Pharmaceutics, 441, 323-333.
798 Dickinson, E. (2009). Hydrocolloids as emulsifiers and emulsion stabilizers. Food
799 Hydrocolloids, 23, 1473-1482.
800 Dickinson, E. (2012). Use of nanoparticles and microparticles in the formation and
801 stabilization of food emulsions. Trends in Food Science & Technology, 24, 4-12.
802 Dickinson, E. (2017). Biopolymer-based particles as stabilizing agents for emulsions and
803 foams. Food Hydrocolloids, 68, 219-231.
804 Fernández-García, E., Carvajal-Lérida, I., & Pérez-Gálvez, A. (2009). In vitro
805 bioaccessibility assessment as a prediction tool of nutritional efficiency. Nutrition
806 Research, 29, 751-760.
807 Fu, T.-J., Abbott, U. R., & Hatzos, C. (2002). Digestibility of food allergens and
808 nonallergenic proteins in simulated gastric fluid and simulated intestinal fluida
809 comparative study. Journal of Agricultural and Food Chemistry, 50, 7154-7160.
810 Fujisawa, S., Atsumi, T., Mariko Ishihara, & Yoshinori Kadoma. (2004). Cytotoxicity, ROS-
811 generation Activity and Radical-scavenging Activity of Curcumin and Related
812 Compounds. Anticancer Research, 24, 563-570.
813 Goel, A., Kunnumakkara, A. B., & Aggarwal, B. B. (2008). Curcumin as “Curecumin”: From
814 kitchen to clinic. Biochemical Pharmacology, 75, 787-809.
815 Goh, K. K. T., Sarkar, A., & Singh, H. (2008). Chapter 12 - Milk protein–polysaccharide
816 interactions. In Milk Proteins (pp. 347-376). San Diego: Academic Press.
817 Goh, K. K. T., Sarkar, A., & Singh, H. (2014). Chapter 13 - Milk Protein–Polysaccharide
818 Interactions. In Milk Proteins (Second edition) (pp. 387-419). San Diego: Academic
819 Press.
820 Gong, C., Wu, Q., Wang, Y., Zhang, D., Luo, F., Zhao, X., Wei, Y., & Qian, Z. (2013). A
821 biodegradable hydrogel system containing curcumin encapsulated in micelles for
822 cutaneous wound healing. Biomaterials, 34, 6377-6387.
823 Hasan, M., Belhaj, N., Benachour, H., Barberi-Heyob, M., Kahn, C. J. F., Jabbari, E., Linder,
824 M., & Arab-Tehrany, E. (2014). Liposome encapsulation of curcumin: Physico-
825 chemical characterizations and effects on MCF7 cancer cell proliferation.
826 International Journal of Pharmaceutics, 461, 519-528.
827 Heger, M., Golen, R. F. v., Broekgaarden, M., & Michel, M. C. (2014). The molecular basis
828 for the pharmacokinetics and pharmacodynamics of curcumin and its metabolites in
829 relation to cancer. Pharmacological Reviews, 66, 222-307.
830 Jagannathan, R., Abraham, P. M., & Poddar, P. (2012). Temperature-dependent
831 spectroscopic evidences of curcumin in aqueous medium: A mechanistic study of its
832 solubility and stability. The Journal of Physical Chemistry B, 116, 14533-14540.

Joung, H. J., Choi, M.-J., Kim, J. T., Park, S. H., Park, H. J., & Shin, G. H. (2016). Development of food-grade curcumin nanoemulsion and its potential application to food beverage system: Antioxidant property and in vitro digestion. Journal of Food Science, 81, N745-N753.

Jovanovic, S. V., Steenken, S., Boone, C. W., & Simic, M. G. (1999). H-atom transfer is a preferred antioxidant mechanism of curcumin. Journal of the American Chemical Society, 121, 9677-9681.

Kakkar, V., Singh, S., Singla, D., & Kaur, I. P. (2011). Exploring solid lipid nanoparticles to enhance the oral bioavailability of curcumin. Molecular Nutrition & Food Research, 55, 495-503.

Khopde, S. M., Indira Priyadarsini, K., Palit, D. K., & Mukherjee, T. (2000). Effect of solvent on the excited-state photophysical properties of curcumin. Photochemistry and Photobiology, 72, 625-631.

Kido, Y., Hiramoto, S., Murao, M., Horio, Y., Miyazaki, T., Kodama, T., & Nakabou, Y. (2003). ∑-Polylysine inhibits pancreatic lipase activity and suppresses postprandial hypertriacylglyceridemia in rats. The Journal of Nutrition, 133, 1887-1891.

Kolev, T. M., Velcheva, E. A., Stamboliyska, B. A., & Spiteller, M. (2005). DFT and experimental studies of the structure and vibrational spectra of curcumin. International Journal of Quantum Chemistry, 102, 1069-1079.

Kumar, A., Kaur, G., Kansal, S. K., Chaudhary, G. R., & Mehta, S. K. (2016). (Cationic+nonionic) mixed surfactant aggregates for solubilisation of curcumin. The Journal of Chemical Thermodynamics, 93, 115-122.

Kurniawansyah, F., Mammucari, R., & Foster, N. R. (2017). Polymorphism of curcumin from dense gas antisolvent precipitation. Powder Technology, 305, 748-756.

Laguna, L., Picouet, P., Guàrdia, M. D., Renard, C. M. G. C., & Sarkar, A. (2017). In vitro gastrointestinal digestion of pea protein isolate as a function of pH, food matrices, autoclaving, high-pressure and re-heat treatments. LWT - Food Science and Technology, 84, 511-519.

Li, J., Hwang, I.-C., Chen, X., & Park, H. J. (2016). Effects of chitosan coating on curcumin loaded nano-emulsion: Study on stability and in vitro digestibility. Food Hydrocolloids, 60, 138-147.

Lin, C.-C., Lin, H.-Y., Chen, H.-C., Yu, M.-W., & Lee, M.-H. (2009). Stability and characterisation of phospholipid-based curcumin-encapsulated microemulsions. Food Chemistry, 116, 923-928.

Liu, J., Svärd, M., Hippen, P., & Rasmuson, Å. C. (2015). Solubility and crystal nucleation in organic solvents of two polymorphs of curcumin. Journal of Pharmaceutical Sciences, 104, 2183-2189.

Liu, Y., & Guo, R. (2008). pH-dependent structures and properties of casein micelles. Biophysical Chemistry, 136, 67-73.

Luo, Z., Murray, B. S., Ross, A.-L., Povey, M. J. W., Morgan, M. R. A., & Day, A. J. (2012). Effects of pH on the ability of flavonoids to act as Pickering emulsion stabilizers. Colloids and Surfaces B: Biointerfaces, 92, 84-90.

Ma, P., Zeng, Q., Tai, K., He, X., Yao, Y., Hong, X., & Yuan, F. (2017a). Preparation of curcumin-loaded emulsion using high pressure homogenization: Impact of oil phase and concentration on physicochemical stability. LWT - Food Science and Technology, 84, 34-46.

Ma, P., Zeng, Q., Tai, K., He, X., Yao, Y., Hong, X., & Yuan, F. (2017b). Preparation of curcumin-loaded emulsion using high pressure homogenization: Impact of oil phase and concentration on physicochemical stability. LWT - Food Science and Technology.

882 Malik, P., Ameta, R. K., & Singh, M. (2016). Physicochemical study of curcumin in oil
883 driven nanoemulsions with surfactants. Journal of Molecular Liquids, 220, 604-622.
884 Marefati, A., Bertrand, M., Sjöö, M., Dejmek, P., & Rayner, M. (2017). Storage and
885 digestion stability of encapsulated curcumin in emulsions based on starch granule
886 Pickering stabilization. Food Hydrocolloids, 63, 309-320.
887 McClements, D. J. (2012a). Crystals and crystallization in oil-in-water emulsions:
888 Implications for emulsion-based delivery systems. Advances in Colloid and Interface
889 Science, 174, 1-30.
890 McClements, D. J. (2012b). Fabrication, characterization and properties of food
891 nanoemulsions. 293-316.
892 McClements, D. J. (2015). Food emulsions: Principles, practices, and techniques: CRC
893 press.
894 McClements, D. J., Decker, E. A., Park, Y., & Weiss, J. (2009). Structural design principles
895 for delivery of bioactive components in nutraceuticals and functional foods. Critical
896 Reviews in Food Science and Nutrition, 49, 577-606.
897 McClements, D. J., & Li, Y. (2010). Structured emulsion-based delivery systems: controlling
898 the digestion and release of lipophilic food components. Adv Colloid Interface Sci,
899 159, 213-228.
900 McClements, D. J., & Rao, J. (2011). Food-grade nanoemulsions: Formulation, fabrication,
901 properties, performance, biological fate, and potential toxicity. Critical Reviews in
902 Food Science and Nutrition, 51, 285-330.
903 McClements, D. J., Saliva-Trujillo, L., Zhang, R., Zhang, Z., Zou, L., Yao, M., & Xiao, H.
904 (2016). Boosting the bioavailability of hydrophobic nutrients, vitamins, and
905 nutraceuticals in natural products using excipient emulsions. Food Research
906 International, 88, 140-152.
907 Minekus, M., Alminger, M., Alvito, P., Ballance, S., Bohn, T., Bourlieu, C., Carriere, F.,
908 Boutrou, R., Corredig, M., Dupont, D., Dufour, C., Egger, L., Golding, M., Karakaya,
909 S., Kirkhus, B., Le Feunteun, S., Lesmes, U., Macierzanka, A., Mackie, A., Marze, S.,
910 McClements, D. J., Menard, O., Recio, I., Santos, C. N., Singh, R. P., Vegarud, G. E.,
911 Wickham, M. S. J., Weitschies, W., & Brodkorb, A. (2014). A standardised static in
912 vitro digestion method suitable for food - an international consensus. Food &
913 Function, 5, 1113-1124.
914 Mishra, M. K., Sanphui, P., Ramamurty, U., & Desiraju, G. R. (2014). Solubility-hardness
915 correlation in molecular crystals: Curcumin and sulfathiazole polymorphs. Crystal
916 Growth & Design, 14, 3054-3061.
917 Pan, K., Zhong, Q., & Baek, S. J. (2013). Enhanced dispersibility and bioactivity of curcumin
918 by encapsulation in casein nanocapsules. Journal of Agricultural and Food
919 Chemistry, 61, 6036-6043.
920 Payton, F., Sandusky, P., & Alworth, W. L. (2007). NMR study of the solution structure of
921 curcumin. Journal of Natural Products, 70, 143-146.
922 Pickering, S. U. (1907). CXCVI.-Emulsions. Journal of the Chemical Society, Transactions,
923 91, 2001-2021.
924 Pinheiro, A. C., Coimbra, M. A., & Vicente, A. A. (2016). In vitro behaviour of curcumin
925 nanoemulsions stabilized by biopolymer emulsifiers – Effect of interfacial
926 composition. Food Hydrocolloids, 52, 460-467.
927 Pinheiro, A. C., Lad, M., Silva, H. D., Coimbra, M. A., Boland, M., & Vicente, A. A. (2013).
928 Unravelling the behaviour of curcumin nanoemulsions during in vitro digestion:
929 Effect of the surface charge. Soft Matter, 9, 3147-3154.

PubChem-969516. PubChem Compound Database; CID=969516. National Center for Biotechnology Information. https://pubchem.ncbi.nlm.nih.gov/compound/969516 (accessed June 26, 2017). In.
Qi, J., Huang, C., He, F., & Yao, P. (2013). Heat-treated emulsions with cross-linking bovine serum albumin interfacial films and different dextran surfaces: Effect of paclitaxel delivery. Journal of Pharmaceutical Sciences, 102, 1307-1317.
Rachmawati, H., Edityaningrum, C. A., & Mauludin, R. (2013). Molecular inclusion complex of curcumin–β-cyclodextrin nanoparticle to enhance curcumin skin permeability from hydrophilic matrix gel. AAPS PharmSciTech, 14, 1303-1312.
Ramsden, W. (1903). Separation of solids in the surface-layers of solutions and 'suspensions' (observations on surface-membranes, bubbles, emulsions, and mechanical coagulation). -- Preliminary account. Proceedings of the Royal Society of London, 72, 156-164.
Rao, P. J., & Khanum, H. (2016). A green chemistry approach for nanoencapsulation of bioactive compound – Curcumin. LWT - Food Science and Technology, 65, 695-702.
Ravindranath, V., & Chandrasekhara, N. (1980). Absorption and tissue distribution of curcumin in rats. Toxicology, 16, 259-265.
Sanphui, P., Goud, N. R., Khandavilli, U. B. R., Bhanoth, S., & Nangia, A. (2011). New polymorphs of curcumin. Chemical Communications, 47, 5013-5015.
Sari, T. P., Mann, B., Kumar, R., Singh, R. R. B., Sharma, R., Bhardwaj, M., & Athira, S. (2015). Preparation and characterization of nanoemulsion encapsulating curcumin. Food Hydrocolloids, 43, 540-546.
Sarkar, A., Goh, K. K. T., & Singh, H. (2009a). Colloidal stability and interactions of milk-protein-stabilized emulsions in an artificial saliva. Food Hydrocolloids, 23, 1270-1278.
Sarkar, A., Goh, K. K. T., & Singh, H. (2010a). Properties of oil-in-water emulsions stabilized by β-lactoglobulin in simulated gastric fluid as influenced by ionic strength and presence of mucin. Food Hydrocolloids, 24, 534-541.
Sarkar, A., Goh, K. K. T., Singh, R. P., & Singh, H. (2009b). Behaviour of an oil-in-water emulsion stabilized by β-lactoglobulin in an in vitro gastric model. Food Hydrocolloids, 23, 1563-1569.
Sarkar, A., Horne, D. S., & Singh, H. (2010b). Interactions of milk protein-stabilized oil-in-water emulsions with bile salts in a simulated upper intestinal model. Food Hydrocolloids, 24, 142-151.
Sarkar, A., Horne, D. S., & Singh, H. (2010c). Pancreatin-induced coalescence of oil-in-water emulsions in an in vitro duodenal model. International Dairy Journal, 20, 589-597.
Sarkar, A., Murray, B., Holmes, M., Ettelaie, R., Abdalla, A., & Yang, X. (2016a). In vitro digestion of Pickering emulsions stabilized by soft whey protein microgel particles: Influence of thermal treatment. Soft Matter, 12, 3558-3569.
Sarkar, A., & Singh, H. (2012). Oral behaviour of food emulsions. In J. Chen & L. Engelen (Eds.), Food Oral Processing (pp. 111-137): Wiley-Blackwell.
Sarkar, A., & Singh, H. (2016). Emulsions and foams stabilised by milk proteins. In P. L. H. McSweeney & J. A. O'Mahony (Eds.), Advanced Dairy Chemistry: Volume 1B: Proteins: Applied Aspects (pp. 133-153). New York, NY: Springer New York.
Sarkar, A., Ye, A., & Singh, H. (2016b). On the role of bile salts in the digestion of emulsified lipids. Food Hydrocolloids, 60, 77-84.
Sarkar, A., Ye, A., & Singh, H. (2017a). Oral processing of emulsion systems from a colloidal perspective. Food & Function, 8, 511-521.

Sarkar, A., Zhang, S., Murray, B., Russell, J. A., & Boxal, S. (2017b). Modulating in vitro gastric digestion of emulsions using composite whey protein-cellulose nanocrystal interfaces. Colloids and Surfaces B: Biointerfaces, 158, 137-146.

Scanff, P., Savalle, B., Miranda, G., Pelissier, J. P., Guilloteau, P., & Toullec, R. (1990). In vivo gastric digestion of milk proteins. Effect of technological treatments. Journal of Agricultural and Food Chemistry, 38, 1623-1629.

Selvam, C., Jachak, S. M., Thilagavathi, R., & Chakraborti, A. K. (2005). Design, synthesis, biological evaluation and molecular docking of curcumin analogues as antioxidant, cyclooxygenase inhibitory and anti-inflammatory agents. Bioorganic & Medicinal Chemistry Letters, 15, 1793-1797.

Setthacheewakul, S., Mahattanadul, S., Phadoongsombut, N., Pichayakorn, W., & Wiwattanapatapee, R. (2010). Development and evaluation of self-microemulsifying liquid and pellet formulations of curcumin, and absorption studies in rats. European Journal of Pharmaceutics and Biopharmaceutics, 76, 475-485.

Shah, B. R., Li, Y., Jin, W., An, Y., He, L., Li, Z., Xu, W., & Li, B. (2016a). Preparation and optimization of Pickering emulsion stabilized by chitosan-tripolyphosphate nanoparticles for curcumin encapsulation. Food Hydrocolloids, 52, 369-377.

Shah, B. R., Zhang, C., Li, Y., & Li, B. (2016b). Bioaccessibility and antioxidant activity of curcumin after encapsulated by nano and Pickering emulsion based on chitosan-tripolyphosphate nanoparticles. Food Research International, 89, 399-407.

Shao, Y., & Tang, C.-H. (2016). Gel-like pea protein Pickering emulsions at pH3.0 as a potential intestine-targeted and sustained-release delivery system for β-carotene. Food Research International, 79, 64-72.

Sharma, R. A., Euden, S. A., Platton, S. L., Cooke, D. N., Shafayat, A., Hewitt, H. R., Marczylo, T. H., Morgan, B., Hemingway, D., Plummer, S. M., Pirmohamed, M., Gescher, A. J., & Steward, W. P. (2004). Phase I Clinical Trial of Oral Curcumin. Biomarkers of Systemic Activity and Compliance, 10, 6847-6854.

Sharma, R. A., Gescher, A. J., & Steward, W. P. (2005). Curcumin: The story so far. European Journal of Cancer, 41, 1955-1968.

Sharma, R. A., McLelland, H. R., Hill, K. A., Ireson, C. R., Euden, S. A., Manson, M. M., Pirmohamed, M., Marnett, L. J., A. J. Gescher, & W. P. Steward. (2001). Pharmacodynamic and pharmacokinetic study of oral curcuma extract in patients with colorectal cancer. Clinical Cancer Research, 7, 1894-1900.

Singh, H., & Sarkar, A. (2011). Behaviour of protein-stabilised emulsions under various physiological conditions. Advances in Colloid and Interface Science, 165, 47-57.

Tapal, A., & Tiku, P. K. (2012). Complexation of curcumin with soy protein isolate and its implications on solubility and stability of curcumin. Food Chemistry, 130, 960-965.

Thorat, A. A., & Dalvi, S. V. (2014). Particle formation pathways and polymorphism of curcumin induced by ultrasound and additives during liquid antisolvent precipitation. CrystEngComm, 16, 11102-11114.

Thorat, A. A., & Dalvi, S. V. (2015). Solid-state phase transformations and storage stability of curcumin polymorphs. Crystal Growth & Design, 15, 1757-1770.

Tikekar, R. V., Pan, Y., & Nitin, N. (2013). Fate of curcumin encapsulated in silica nanoparticle stabilized Pickering emulsion during storage and simulated digestion. Food Research International, 51, 370-377.

Tokle, T., Mao, Y., & McClements, D. J. (2013). Potential biological fate of emulsion-based delivery systems: Lipid particles nanolaminated with lactoferrin and β-lactoglobulin coatings. Pharmaceutical Research, 30, 3200-3213.

Tønnesen, H. H., & Karlsen, J. (1985). Studies on curcumin and curcuminoids. Zeitschrift für Lebensmittel-Untersuchung und Forschung, 180, 402-404.

1029 Tønnesen, H. H., Karlsen, J., & Mostad, A. (1982). Structural studies of curcuminoids. I. The
1030 crystal structure of curcumin. Acta Chemica Scandinavica, 36b, 475-479.
1031 Tønnesen, H. H., Karlsen, J., & van Henegouwen, G. B. (1986). Studies on curcumin and
1032 curcuminoids. VIII. Photochemical stability of curcumin. Zeitschrift für Lebensmittel-
1033 Untersuchung und Forschung, 183, 116-122.
1034 Tønnesen, H. H., Másson, M., & Loftsson, T. (2002). Studies of curcumin and curcuminoids.
1035 XXVII. Cyclodextrin complexation: solubility, chemical and photochemical stability.
1036 International Journal of Pharmaceutics, 244, 127-135.
1037 Vecchione, R., Quagliariello, V., Calabria, D., Calcagno, V., De Luca, E., Iaffaioli, R. V., &
1038 Netti, P. A. (2016). Curcumin bioavailability from oil in water nano-emulsions: In
1039 vitro and in vivo study on the dimensional, compositional and interactional
1040 dependence. Journal of Controlled Release, 233, 88-100.
1041 Wang, C., Liu, Z., Xu, G., Yin, B., & Yao, P. (2016). BSA-dextran emulsion for protection
1042 and oral delivery of curcumin. Food Hydrocolloids, 61, 11-19.
1043 Wang, X., Jiang, Y., Wang, Y.-W., Huang, M.-T., Ho, C.-T., & Huang, Q. (2008). Enhancing
1044 anti-inflammation activity of curcumin through O/W nanoemulsions. Food
1045 Chemistry, 108, 419-424.
1046 Wang, Y.-J., Pan, M.-H., Cheng, A.-L., Lin, L.-I., Ho, Y.-S., Hsieh, C.-Y., & Lin, J.-K.
1047 (1997). Stability of curcumin in buffer solutions and characterization of its
1048 degradation products. Journal of Pharmaceutical and Biomedical Analysis, 15, 1867-
1049 1876.
1050 Xiao, J., Li, C., & Huang, Q. (2015). Kafirin nanoparticle-stabilized pickering emulsions as
1051 oral delivery vehicles: Physicochemical stability and in vitro digestion profile.
1052 Journal of Agricultural and Food Chemistry, 63, 10263-10270.
1053 Xiao, J., Wang, X., Gonzalez, A. J. P., & Huang, Q. (2016). Kafirin nanoparticles-stabilized
1054 Pickering emulsions: Microstructure and rheological behavior. Food Hydrocolloids,
1055 54, 30-39.
1056 Xiao, J., Wang, X. a., Perez Gonzalez, A. J., & Huang, Q. (2016). Kafirin nanoparticles-
1057 stabilized Pickering emulsions: Microstructure and rheological behavior. Food
1058 Hydrocolloids, 54, Part A, 30-39.
1059 Xu, D., Zhang, J., Cao, Y., Wang, J., & Xiao, J. (2016). Influence of microcrystalline
1060 cellulose on the microrheological property and freeze-thaw stability of soybean
1061 protein hydrolysate stabilized curcumin emulsion. LWT - Food Science and
1062 Technology, 66, 590-597.
1063 Xu, G., Wang, C., & Yao, P. (2017). Stable emulsion produced from casein and soy
1064 polysaccharide compacted complex for protection and oral delivery of curcumin.
1065 Food Hydrocolloids, 71, 108-117.
1066 Yu, H., & Huang, Q. (2010). Enhanced in vitro anti-cancer activity of curcumin encapsulated
1067 in hydrophobically modified starch. Food Chemistry, 119, 669-674.
1068 Yusoff, A., & Murray, B. S. (2011). Modified starch granules as particle-stabilizers of oil-in-
1069 water emulsions. Food Hydrocolloids, 25, 42-55.
1070 Zhang, R., & McClements, D. J. (2016). Enhancing nutraceutical bioavailability by
1071 controlling the composition and structure of gastrointestinal contents: Emulsion-based
1072 delivery and excipient systems. Food Structure, 10, 21-36.
1073 Zhao, Z., Xie, M., Li, Y., Chen, A., Li, G., Zhang, J., Hu, H., Wang, X., & Li, S. (2015).
1074 Formation of curcumin nanoparticles via solution-enhanced dispersion by
1075 supercritical CO(2). International Journal of Nanomedicine, 10, 3171-3181.
1076 Zheng, B., Zhang, Z., Chen, F., Luo, X., & McClements, D. J. (2017). Impact of delivery
1077 system type on curcumin stability: Comparison of curcumin degradation in aqueous
1078 solutions, emulsions, and hydrogel beads. Food Hydrocolloids, 71, 187-197.

Zou, L., Liu, W., Liu, C., Xiao, H., & McClements, D. J. (2015a). Utilizing food matrix effects to enhance nutraceutical bioavailability: increase of curcumin bioaccessibility using excipient emulsions. J Agric Food Chem, 63, 2052-2062.
Zou, L., Zheng, B., Liu, W., Liu, C., Xiao, H., & McClements, D. J. (2015b). Enhancing nutraceutical bioavailability using excipient emulsions: Influence of lipid droplet size on solubility and bioaccessibility of powdered curcumin. Journal of Functional Foods, 15, 72-83.
Zou, L., Zheng, B., Zhang, R., Zhang, Z., Liu, W., Liu, C., Zhang, G., Xiao, H., & McClements, D. J. (2016). Influence of lipid phase composition of excipient emulsions on curcumin solubility, stability, and bioaccessibility. Food Biophysics, 11, 213-225.

Figure Captions

Figure 1. Functional groups in curcumin.

Figure 2. Scanning electron micrographs (SEM) of curcumin crystals dispersed at 10 mg/ mL in methanol (a), DMSO (b), and sunflower oil (c) in lower (×5,000, left) and higher magnifications (×10,000, right).

Figure 3. Schematic diagram of conventional emulsion (a), multilayered emulsion (b) and Pickering emulsion (c). Preparation method of conventional and Pickeing emuslion (a) and multilayered emuslion (e).

Figure 4. Schematic diagram of nanoemulsion (a) and its preparation method by high-intensity (b) and low-intesity (c) techniques.

Figure 1.

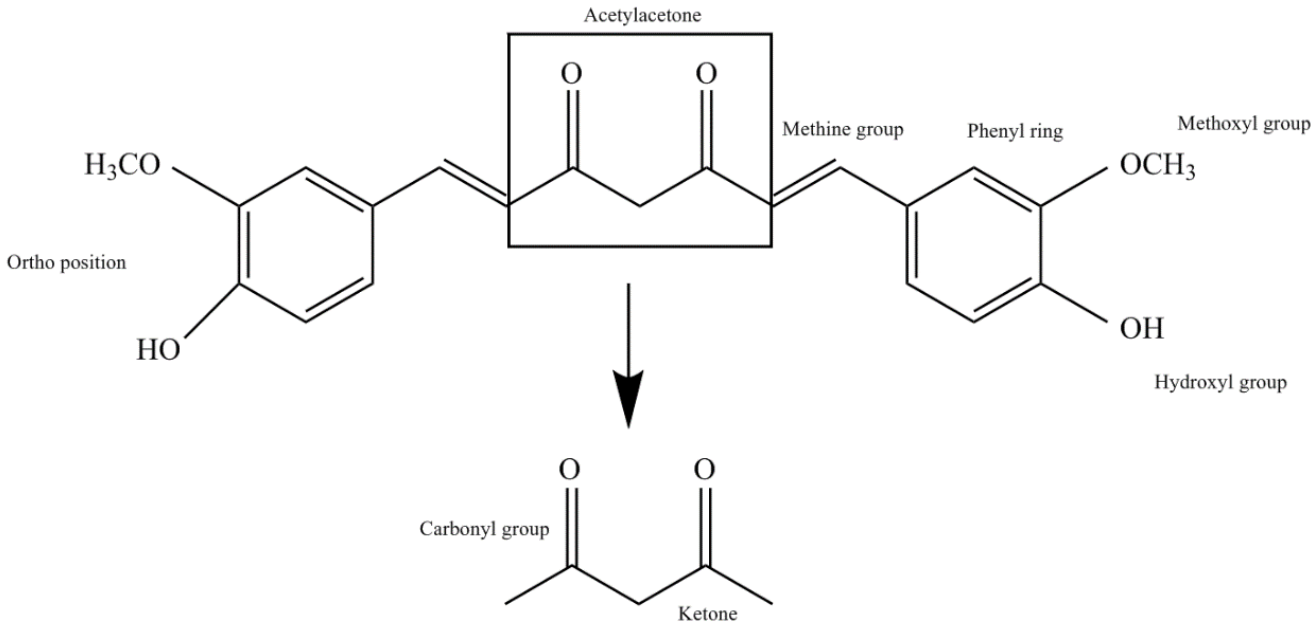

Acetylacetone
O
O
Methine group
Phenyl ring
Methoxyl group
H_3CO
OCH_3
Ortho position
HO
OH
Hydroxyl group
O
O
Carbonyl group
Ketone

Figure 2.

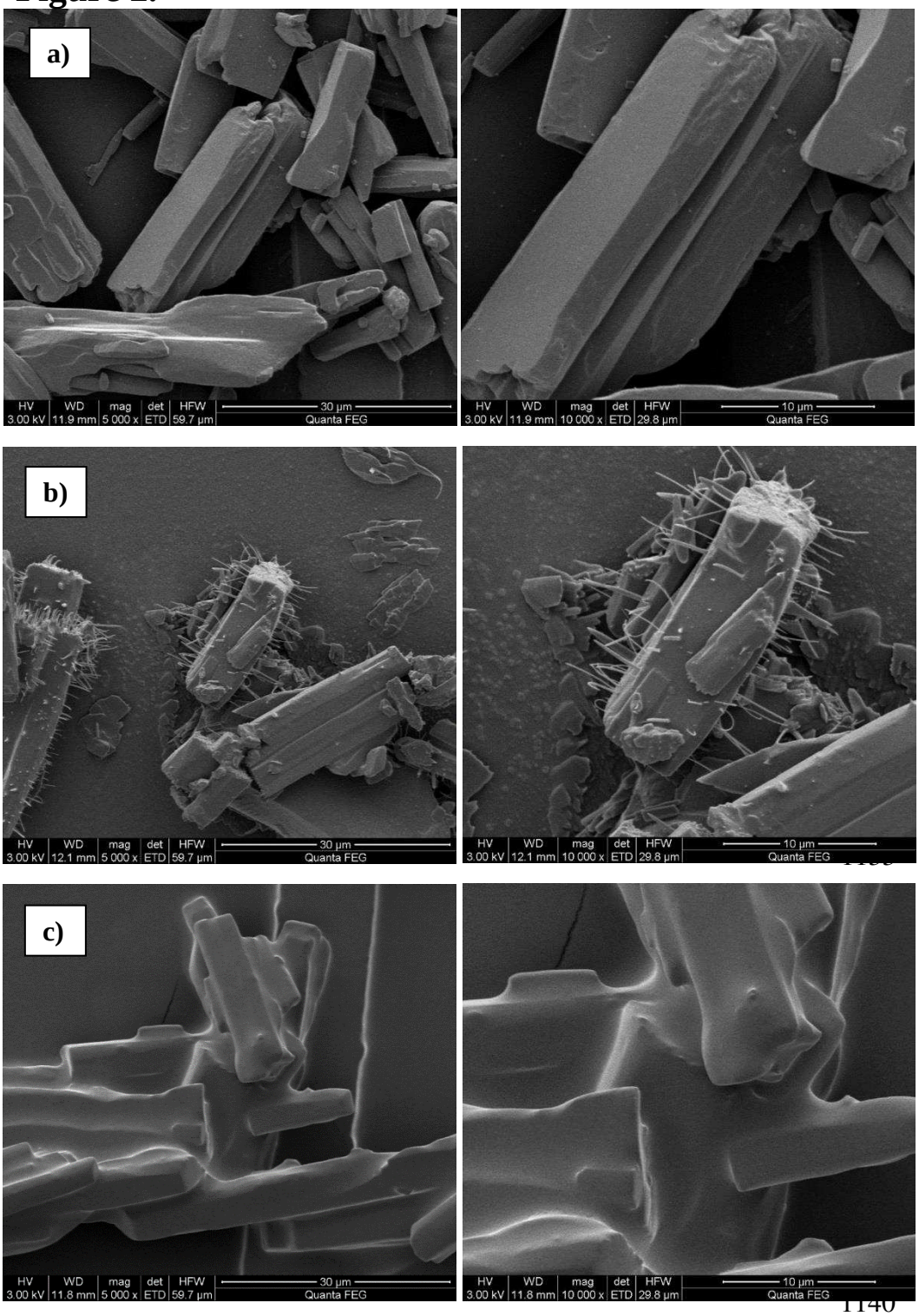

a)
HV 3.00 kV | WD 11.9 mm | mag 5 000 x | det ETD | HFW 59.7 µm | 30 µm | Quanta FEG
HV 3.00 kV | WD 11.9 mm | mag 10 000 x | det ETD | HFW 29.8 µm | 10 µm | Quanta FEG
b)
HV 3.00 kV | WD 12.1 mm | mag 5 000 x | det ETD | HFW 59.7 µm | 30 µm | Quanta FEG
HV 3.00 kV | WD 12.1 mm | mag 10 000 x | det ETD | HFW 29.8 µm | 10 µm | Quanta FEG
c)
HV 3.00 kV | WD 11.8 mm | mag 5 000 x | det ETD | HFW 59.7 µm | 30 µm | Quanta FEG
HV 3.00 kV | WD 11.8 mm | mag 10 000 x | det ETD | HFW 29.8 µm | 10 µm | Quanta FEG

Figure 3.

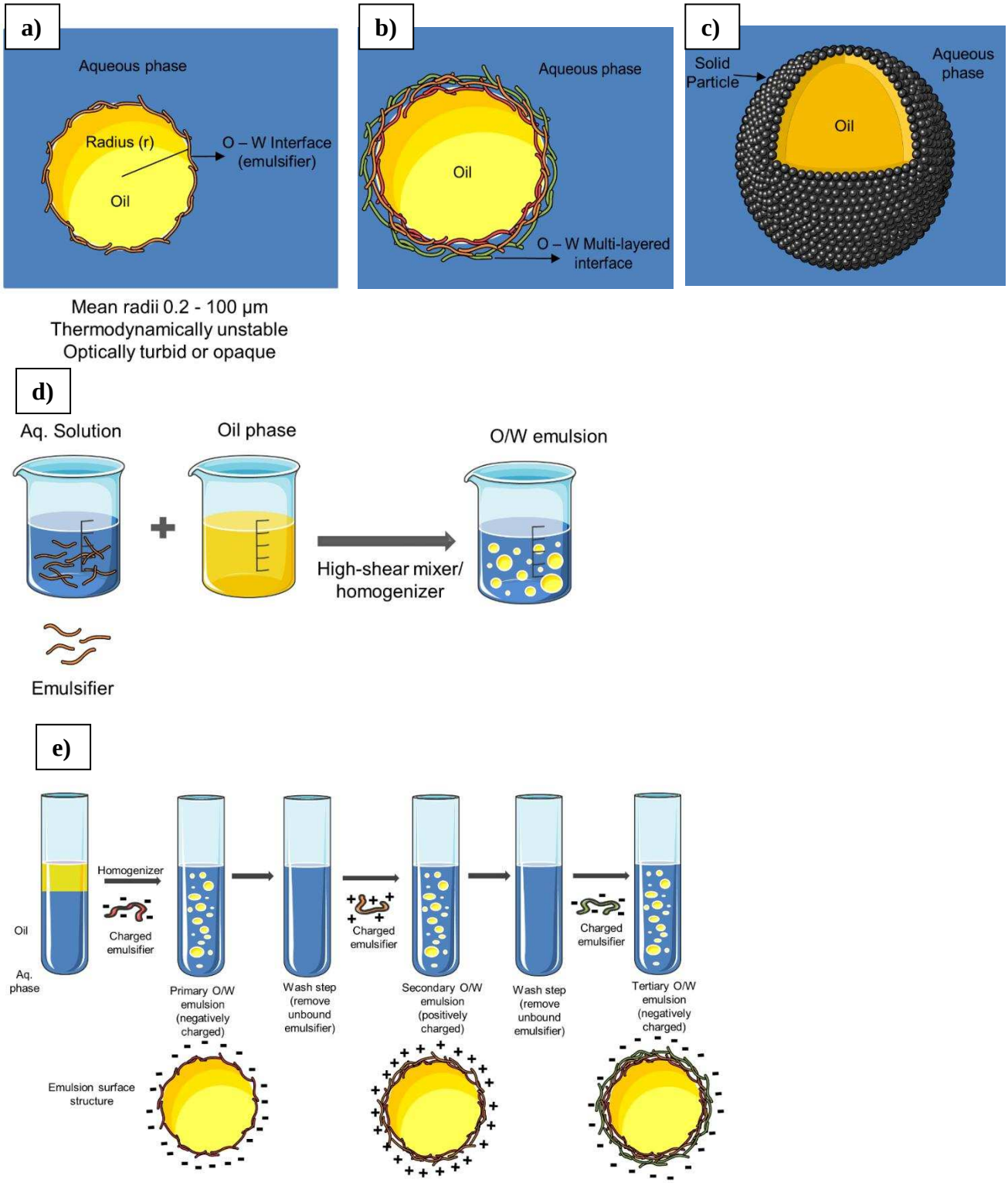
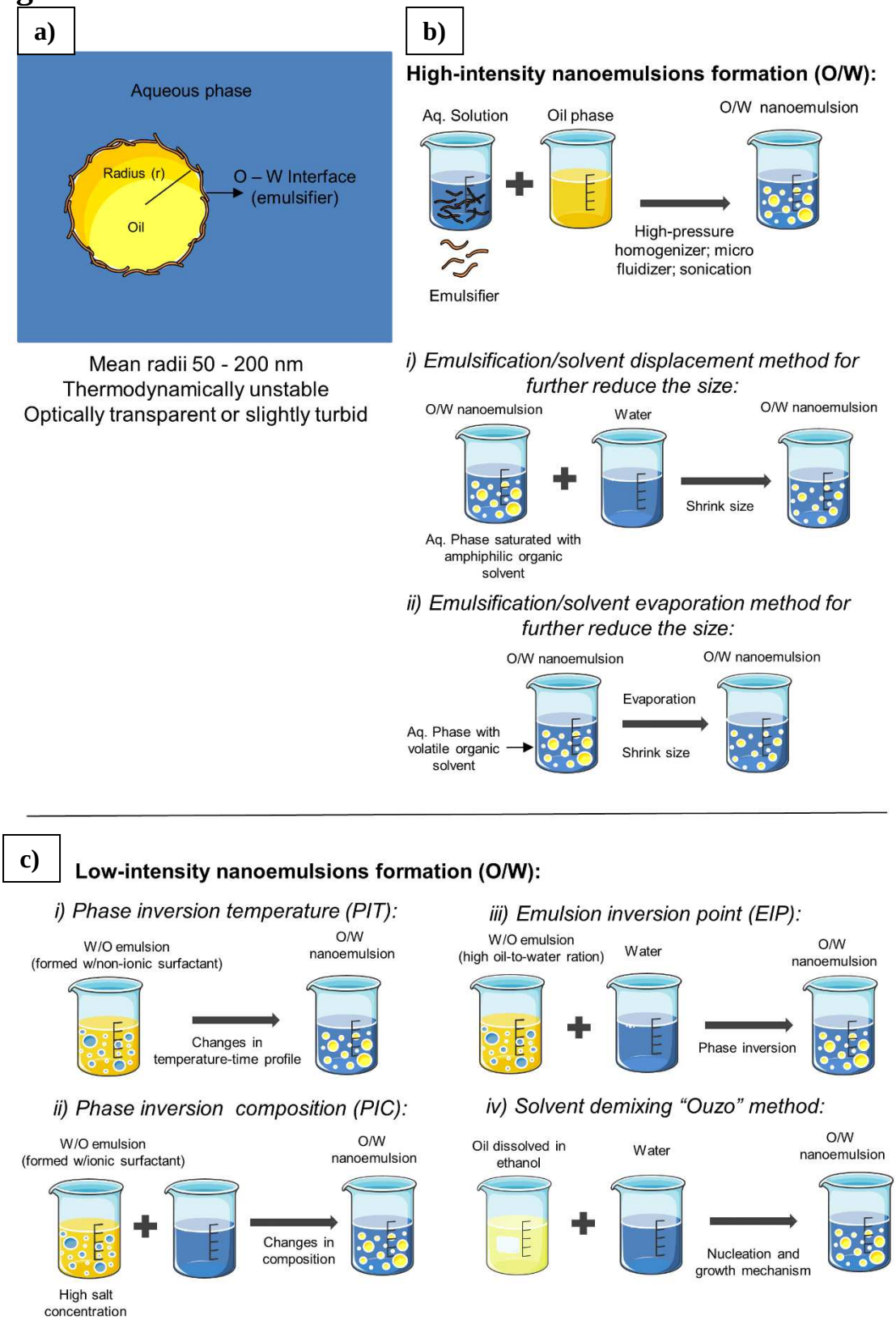

a)
Aqueous phase
Radius (r)
O – W Interface (emulsifier)
Oil
b)
Aqueous phase
Oil
O – W Multi-layered interface
c)
Solid Particle
Aqueous phase
Oil
Mean radii 0.2 - 100 µm
Thermodynamically unstable
Optically turbid or opaque
d)
Aq. Solution
Oil phase
O/W emulsion
High-shear mixer/ homogenizer
Emulsifier
e)
Oil
Aq. phase
Homogenizer
Charged emulsifier
Primary O/W emulsion (negatively charged)
Wash step (remove unbound emulsifier)
Charged emulsifier
Secondary O/W emulsion (positively charged)
Wash step (remove unbound emulsifier)
Charged emulsifier
Tertiary O/W emulsion (negatively charged)
Emulsion surface structure

Figure 4.


a)
Aqueous phase
Radius (r)
O – W Interface
(emulsifier)
Oil
Mean radii 50 - 200 nm
Thermodynamically unstable
Optically transparent or slightly turbid
b)
High-intensity nanoemulsions formation (O/W):
Aq. Solution
Oil phase
O/W nanoemulsion
High-pressure
homogenizer; micro
fluidizer; sonication
Emulsifier
i) Emulsification/solvent displacement method for
further reduce the size:
O/W nanoemulsion
Water
O/W nanoemulsion
Shrink size
Aq. Phase saturated with
amphiphilic organic
solvent
ii) Emulsification/solvent evaporation method for
further reduce the size:
O/W nanoemulsion
O/W nanoemulsion
Evaporation
Aq. Phase with
volatile organic
solvent
Shrink size
c)
Low-intensity nanoemulsions formation (O/W):
i) Phase inversion temperature (PIT):
W/O emulsion
(formed w/non-ionic surfactant)
O/W
nanoemulsion
Changes in
temperature-time profile
iii) Emulsion inversion point (EIP):
W/O emulsion
(high oil-to-water ration)
Water
O/W
nanoemulsion
Phase inversion
ii) Phase inversion composition (PIC):
W/O emulsion
(formed w/ionic surfactant)
O/W
nanoemulsion
Changes in
composition
High salt
concentration
iv) Solvent demixing “Ouzo” method:
Oil dissolved in
ethanol
Water
O/W
nanoemulsion
Nucleation and
growth mechanism

Tables

Table 1. Solubility (μg/mL) of curcumin in various edible oils.

Oil	Solubility (μg/mL)	Curcumin dispersion conditions	References
Corn oil	7580	AT/ 48 h	(Setthacheewakul, et al., 2010)
	70	60 °C/ 10 min, 20 min sonication	(Joung, et al., 2016)
	2.76	60 °C/ 10 min, 20 min sonication	(Ahmed, et al., 2012)
Soybean oil	7380	AT/ 48 h	(Setthacheewakul, et al., 2010)
	0.1834	AT/ 10 min	(Lin, et al., 2009)
Oleic acid	1390	AT/ 48 h	(Setthacheewakul, et al., 2010)
MCT	250	60 °C/ 10 min, 20 min sonication	(Joung, et al., 2016)
	7.505	60 °C/ 10 min, 20 min sonication	Ahmed, et al. (2012)
Ethyl oleate	310.59	37°C/ 24 h	(Cui, et al., 2009)
	12170	AT/ 48 h	(Setthacheewakul, et al., 2010)
	0.348	AT/ 10 min	(Lin, et al., 2009)
Peppermint oil	0.2694	AT/ 10 min	(Lin, et al., 2009)
Peanut oil	129.22	37°C/ 24 h	(Cui, et al., 2009)
Castor oil	256.59	37°C/ 24 h	(Cui, et al., 2009)
Coconut oil	100	60 °C/ 10 min, 20 min sonication	(Joung, et al., 2016)
Olive oil	80	60 °C/ 10 min, 20 min sonication	(Joung, et al., 2016)

Abbreviations: AT, ambient temperature; MCT, medium chain triacylglycerol.

Table 2. Composition and formation of nanoemulsions for delivery of curcumin.

Emulsifier(s)	Oil (wt%)	Curcumin loading in oil phase (wt%)	Curcumin dispersion method	Emulsification process	References
Octenyl-succinic-anhydride (OSA) modified starch, OSA modified starch - coated with chitosan or sodium carboxymeth yl cellulose	MCT (0.02-0.14)	0.00028 – 0.0020	Magnetic stirring (100 ºC, 7 min)	High-speed blender (14,000 rpm, 2 min/ High-intensity sonication (20 kHz, 1-13 min, 40-45 ºC).	(Abbas, et al., 2014; Abbas, et al., 2015)
Hydrogenated L-α-phosphatidylc holine (HEPC) (surfactant), Tween 80 and Polyoxyethyl ene hydrogenated castor oil 60 (co-surfactant)	Soybean Oil (~3)	0.041 – 0.66	Curcumin initially dissolved in chloroform, then oil, evaporation of chloroform	Rotary evaporation, vacuum desiccation (3-5 h) / Hydrate in bath type sonicator (55-60 ºC) / Vigorous mixing and sonication (5 min) / Sonication (30-60 min, N_2 atmosphere, 55-60 ºC).	(Anuchapreeda, Fukumori, Okonogi, & Ichikawa, 2012b)
β-lactoglobulin	LCT, MCT, SCT, LCT: SCT (10)	0.15	Magnetic stirring (60ºC, 10 min, 20 min sonication)	High-speed blender (2 min) / High-pressure homogenizer (9,000 psi, 5 cycles)	Ahmed, et al. (2012)
Tween 20, 60 and 80	Soybean oil (10-20)	0.03, 0.07, 0.1	Magnetic stirring (15 min)	Peristaltic pump (mechanical stirring 300-500 rpm) / 30 min (Inversion point (EIP) method	(Borrin, et al., 2016)
Tween 20	Olive Oil, Coconut oil, Corn Oil and MCT (1.9-55.5)	0.3	-	High-speed homogenizer (13500 rpm, 15 min) / High-pressure homogenizer (1,000 bar, 5 cycles).	(Joung, et al., 2016)

Tween 80 (surfactant), lecithin (co-surfactant) – coated with high, medium and low molecular-weight chitosan	MCT (10)	0.65	Heating and stirring (overnight)	Stirring (10 min) / High-speed blender (1600 rpm, 5 min) / Ultrasonication (20 min, 150 W).	(Li, et al., 2016)
Tween 80, lecithin, Acacia gum and whey protein	MCT, Canola Oil, Linseed Oil, Sunflower Oil (0.5 – 3)	1.18	Ultra-sonication	High-speed blender (6 min, 10000 rpm) / High-pressure homogenizer (60 MPa, 3 cycles)	(Ma, et al., 2017a)
Poloxamer-407, Tween 20, Sodium dodecyl sulphate (SDS), Dodecyltrimethylammonium bromide (DTAB)	Cottonseed Oil (0.0010 - 0.0.0048*)	0.220 - 1.099*	Magnetic stirring (70ºC, 1000 rpm)	Magnetic stirring (~70 ºC, 1,000 rpm) / Magnetic stirring (650 rpm, 45 min).	(Malik, Ameta, & Singh, 2016)
Lactoferrin, lactoferrin coated with alginate, Tween 20 (T20), sodium dodecyl sulphate (SDS) and dodecyltrimethylammonium bromide (DTAB)	Corn oil (5)	0.1	-	High-speed blender (2 min) / High-pressure or Microfluidizer (20,000 psi, 5-20 cycles).	(Pinheiro, et al., 2016; Pinheiro, et al., 2013)
Sodium caseinate	Milk fat (1)	0.05	-	Sonication (60 ºC, 5 min) / Sonication (30 min) / Spray dried	(Rao & Khanum, 2016)
Tween 80 (surfactant), whey protein concentrate	MCT (0.5-2)	0.0047 – 0.075	-	Magnetic stirring/ Sonication	(Sari, et al., 2015)

70 (co-surfactant)					
Phosphatidylcholine 80%, coated with chitosan and chitosan 2-iminothiolane conjugate	Soybean Oil (24)	2.2	High-speed blender (60 ºC, 500 rpm), Sonication	Sonication / High-pressure homogenization (2,000 bar).	(Vecchione, et al., 2016)
Tween 20	MCT (10)	1	-	High-speed homogenizer (10 min) or high-pressure homogenizer (6 cycles)	(Wang, et al., 2008)
Papain hydrolysate soy protein isolate (SPIH) – coated with microcrystalline cellulose (MCC)	MCT (10)	0.1	-	Two-speed hand-held homogenizer (3 min) / Microfluidizer (50 MPa, 3 cycles)	(Xu, Zhang, Cao, Wang, & Xiao, 2016)

* mol/kg.
Abbreviations: NE, nanoemulsion

Table 3. Composition and formation of conventional emulsions (protein-polysaccharide conjugates/ complexes-stabilized) and Pickering emulsions (particle-stabilized systems) for delivery of curcumin.

Emulsifier(s)	Oil (wt%)	Curcumin loading in oil phase (wt%)	Curcumin dispersion method	Emulsification process	References
Tween 80	Corn oil (10)	0.00279	Stirring (85 °C, 2 h)	High shear mixer / High-pressure homogenizer (12,000 psi, 5 cycles)	(Zheng, Zhang, Chen, Luo, & McClements, 2017)
Bovine serum albumin - dextran conjugate (BSA-dextran)	MCT (20 or 40)	0.22 - 0.56	Heating (90 °C, dark, 1 h)	Homogenizer (10,000 rpm, 1 min) / High-pressure homogenizer (900 bar, 4 min) / Samples heated (90 °C, dark, 1 h)	(Wang, et al., 2016)
Casein - soybean soluble polysaccharide complex (CN/SSPS)	MCT (16.7)	0.15	Solutions of 10% ethanol, 90% MCT	Homogenizer (10,000 rpm, 1 min) / High-pressure homogenizer (800 bar, 4 min)	(Xu, et al., 2017)
Particles					
Kafirin	Vegetable Oil (0.2 - 0.8)	0.0005 – 0.002	-	High-speed homogenizer (13,000 rpm, 3 min)	(Xiao, et al., 2015)
OSA quinoa starch granules	MCT (7)	0.0016	Rotor-stator high-shear homogenizer (22,000 rpm, 20 min)	High-shear homogenizer (22,000 rpm, 20 and 70 °C, 30 s)	(Marefati, et al., 2017)
Chitosan-tripolyphosphate nanoparticles	MCT and LCT (5-50)	0.1	-	Stirring overnight / High-speed blender (10,000 rpm, 3 min)	(Shah, et al., 2016a; Shah, et al., 2016b)
Colloidal silica	Canola Oil (5)	0.0046	Vigorously mixed (20 min)	Hand-held dispenser (8,000 rpm) / Single-stage homogenizer (600 bar)	(Tikekar, et al., 2013)