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Stability of curcumin in oil-in-water emulsions: Impact of emulsifier type and concentration on chemical degradation

Mahesh Kharat, Guodong Zhang, David Julian McClements*

Department of Food Science, University of Massachusetts Amherst, Amherst, MA 01003, USA

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ABSTRACT

Oral ingestion of curcumin is claimed to be effective against several diseases, including inflammation and cancer. However, its utilization in food, supplement, and pharmaceutical products is often challenging due to its poor water solubility, high chemical instability, and limited oral bioavailability. Emulsion-based delivery systems can be designed to overcome these challenges, but their composition and structure must be optimized to ensure they function appropriately. This study examined the impact of emulsifier type on the formation and stability of curcumin-loaded oil-in-water emulsions: sodium caseinate; Tween 80; quillaja saponin; gum arabic. The effectiveness of these food-grade emulsifiers at forming emulsions by microfluidization was characterized in terms of their surface load, i.e., the mass of emulsifier per unit surface area. The surface loads decreased in the following order: gum arabic (55.3 mg/m^2) > > saponins (2.0 mg/m^2) > Tween 80 (1.6 mg/m^2) > caseinate (1.5 mg/m^2), which indicated that much more gum arabic was required to form emulsions than the other emulsifiers. Curcumin-loaded emulsions were then prepared under conditions where there was just enough emulsifier to cover the droplet surfaces ("critical"), and under conditions where there was an excess of emulsifier in the aqueous phase ("excess"). Initially, both critical and excess emulsions were physically stable and had similar appearances. In all emulsions, curcumin degradation during storage occurred more rapidly at pH 7 than at pH 3, and was faster at 55 °C than at 37 °C. The physical and chemical stability of the curcumin-loaded emulsions also depended on emulsifier type. After storage at 55 °C for 15 days, the extent of curcumin degradation decreased in the following order: saponins > > gum arabic ≈ casinate ≈ Tween 80. Moreover, droplet creaming was observed in the critical Tween 80 and saponin emulsions, but not in the other emulsions. These results suggest that saponin accelerated curcumin degradation, possibly due to its ability to promote peroxidation reactions. Emulsifier concentration did not significantly affect curcumin degradation. These results suggest that the physical and chemical stability of curcumin-loaded emulsions is influenced by emulsifier type and level. This information may be useful for formulating emulsion-based delivery systems for curcumin with improved physicochemical and functional properties.

1. Introduction

Curcumin is one of the most widely studied nutraceuticals in the food, supplement, and pharmaceutical areas, and there have been numerous clinical trials conducted on its potential efficacy (Schneider, Gordon, Edwards, & Luis, 2015). This polyphenol is naturally present in the spice turmeric (*Curcuma longa*) along with three other forms demethoxycurcumin, bisdemethoxycurcumin, and cyclocurcumin, which are collectively called curcuminoids and make up about 3–5% of the rhizome (Goel, Kunnumakkara, & Aggarwal, 2008). Turmeric has a long history of utilization in foods, cosmetics, and herbal remedies, especially in Asian countries (Hatcher, Planalp, Cho, Tortia, & Torti, 2008). Numerous health benefits have been claimed for curcumin, including anticancer, antioxidant, anti-Alzheimer's, and anti-inflammatory activities (Naksuriya, Okonogi, Schiffelers, & Hennink, 2014; Shen & Ji, 2012). However, there is still not a clear understanding of its mechanisms of action, and of the contributions of different curcuminoids and their metabolites to the observed pharmacological effects (Shen & Ji, 2012). For instance, it has been reported that the oxidation products of curcumin are much less effective against cancer cell proliferation and inflammation than the parent molecule (Sanidad, Zhu, Wang, Du, & Zhang, 2016). Chemically, curcumin can accept and donate H-bonds, bind cations, and participate in the Michael reaction, which means that it can interact with a wide range of molecular targets linked to chronic diseases (Heger, van Golen, Broekgaarden, & Michel, 2014). Moreover, curcumin exhibits a low level of toxicity, even when

* Corresponding author.
E-mail address: mcclements@foodsci.umass.edu (D.J. McClements).

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consumed at relatively high levels, which suggests that it should be safe to use as a nutraceutical in foods, supplements, and drugs (Lao et al., 2006). Curcumin has even been shown to be effective against various disease markers when used at relatively low concentrations. For instance, a study showed that 16 out of 29 human myeloma cell lines screened exhibited a 50% lethal concentration (LD_{50}) of < 20.5 μM curcumin (Gomez-Bougie et al., 2015).

Although curcumin may be effective against a number of potential diseases, there are several challenges to achieving these potential benefits (Araiza-Calahorra, Akhtar, & Sarkar, 2018). Curcumin is a strongly hydrophobic molecule with a low water-solubility of around 3×10^{-8} M and a high partition coefficient (log *P*) value of around 2.4 (Jankun et al., 2006; Tomren, Masson, Loftsson, & Tonnesen, 2007; Tonnesen, Masson, & Loftsson, 2002). The chemical stability of curcumin depends on its molecular environment, with more rapid chemical degradation occurring under neutral or basic conditions than under acidic conditions, and when it is dispersed in water rather than in oil (Kharat, Du, Zhang, & McClements, 2017; Schneider et al., 2015; Wang et al., 1997). Curcumin has also been reported to have poor permeability through the intestinal mucosa due to cellular accumulation and in-transit degradation (Wahlang, Pawar, & Bansal, 2011). Moreover, after absorption, curcumin is chemically transformed in the blood and extensively metabolized in the liver and other organs (Marczylo, Steward, & Gescher, 2009; Pan, Huang, & Lin, 1999). Overall, these effects lead to a relatively low amount of bioactive curcumin actually reaching the intended site of action.

Numerous approaches have been proposed to enhance the chemical stability of curcumin in food matrices and in the gastrointestinal tract (GIT) so as to improve its oral bioavailability (McClements & Xiao, 2017; Nayak, Mills, & Norton, 2016). Inclusion of curcumin within small hydrophobic particles, such as the lipid droplets in oil-in-water emulsions, improves its water-dispersibility and chemical stability in food matrices (Araiza-Calahorra et al., 2018; Kharat et al., 2017). Encapsulation of curcumin within the hydrophobic core of lipid droplets also protects curcumin from chemical degradation in aqueous environments, and improves its bioaccessibility under simulated GIT conditions (Zou et al., 2016; Zou, Liu, Liu, Xiao, & McClements, 2015). The bioaccessibility of curcumin in oil-in-water emulsions has been reported to depend on the chain length of the lipid phase with medium-chain triglycerides giving a higher value than short- or long-chain triglycerides (Ahmed, Li, McClements, & Xiao, 2012). It has also been reported that emulsified curcumin had a higher anti-inflammatory activity than curcumin in solution, which highlights the importance of the physical dimensions of the lipid phase (Wang et al., 2008). Our previous study showed that degradation of curcumin in MCT-in-water emulsions was pH dependent with about 62% curcumin retention after 1 month when emulsions were stored at 37 °C (Kharat et al., 2017).

The ability of an emulsion to act as a good oral delivery system for curcumin depends on its composition and structure (Araiza-Calahorra et al., 2018). Consequently, it is important to optimize these parameters in order to develop effective delivery systems that can be utilized in a range of food and other products. The purpose of the current study was to examine the impact of emulsifier type on the formation and stability of curcumin-loaded oil-in-water emulsions. A variety of synthetic and natural emulsifiers are available for application in food products (Hartel & Hasenhuettl, 2013). However, there is growing interest in the use of natural emulsifiers in the food industry due to consumer concerns about health, environmental, and sustainability issues (McClements & Gumus, 2016). In this study, we therefore compared the efficacy of three natural emulsifiers (sodium caseinate, gum arabic, and quillaja saponins) at forming and stabilizing curcumin-loaded emulsions with a commonly used synthetic surfactant (Tween 80). A highly pure form of curcumin, which was synthesized and purified in our laboratories, was used in this study to facilitate the interpretation of the results, rather than a complex mixture of curcuminoids.

2. Materials and methods

2.1. Materials

Synthesis and purification of curcumin was carried out in the Department of Food Science at the University of Massachusetts using a method reported previously (Pabon, 1964). Medium chain triglyceride (MCT) oil was obtained from Warner Graham Co. (Cockeysville, MD), which was reported to mainly consist of caprylic (58.1%), and capric (41%) acids. Dimethyl sulfoxide (DMSO), sodium hydroxide (NaOH), sodium phosphate anhydrous dibasic, and potassium phosphate monobasic were obtained from Fisher Scientific (Fair Lawn, NJ). Sodium azide, hydrochloric acid (HCl), gum arabic (GA), and Tween 80 (T80), were purchased from the Sigma-Aldrich Company (St. Louis, MO). Sodium salt of casein (NaC) was product from MP Biomedicals (Solon, OH). Foamation® QB Dry (SAP), a spray dried purified aqueous *Quillaja saponaria* extract, was obtained from Ingredion Inc. (Westchester, IL). The manufacturer reported that this ingredient had a saponin content between 10 and 30 wt%, with the remainder being mainly maltodextrin and fish gelatin (as processing aids). All solvents and reagents were of analytical grade. Double distilled water from a water purification system (Nanopure Infinity, Barnstaeas International, Dubuque, IA) was used throughout the experiments.

2.2. Determination of emulsifier surface load

First, an aqueous phase was prepared by mixing emulsifier (NaC, T80, SAP, or GA) in phosphate buffer (10 mM, pH 7.0) until a clear solution was obtained. For the GA, the solution was then centrifuged twice at 36,000 ×*g* for 1 h (Thermo Scientific, Waltham, MA) prior to utilization to remove a small amount of insoluble fraction. To prepare stock emulsions, both MCT oil and aqueous phase were mixed together for 2 min using a high-speed blender (M133/1281-0, Biospec Products, Inc., ESGC, Switzerland). The resulting coarse emulsion was then passed through a single-channel microfluidizer (M110L, Microfluidics, Newton, MA) at an operating pressure of 12,000 psi for 5 passes. The emulsifier-to-oil (E:O) ratio in the final emulsions ranged from 0.01 to 2.00. All operations were carried out at ambient temperature (~25 °C).

2.3. Preparation of curcumin-loaded emulsions

To prepare curcumin-loaded emulsions, an oil phase was prepared by dissolving powdered curcumin into MCT oil at a level of 1 mg curcumin per gram of MCT oil. The resulting mixture was heated to 60 °C and stirred at 1200 rpm for 2 h, and then sonicated for 20 mins. This process was repeated if needed to ensure complete solubilization of curcumin in the oil phase. Emulsions were then prepared using the process described in the previous section. After preparation, sodium azide solution was added as an antimicrobial agent, and the emulsions were adjusted to either pH 3 or 7 using HCl and/or NaOH (0.01, 0.1, or 1 N). Finally, the emulsions were diluted with phosphate buffer of the appropriate pH to obtain the final emulsions. The final emulsions contained 9.0 wt% MCT oil, 0.02 wt% sodium azide, and had emulsifier concentrations of 0.5, 0.6, 0.8, and 10.0 wt% for caseinate, Tween 80, saponin, and gum arabic, respectively. These emulsifier levels were selected because they represent the values where the oil droplets surfaces were fully saturated with emulsifier, and small droplets were obtained (Section 3.1).

To study if excess emulsifier affected curcumin stability, another set of emulsions was prepared that contained twice the amount of emulsifier in the aqueous phase. These emulsions therefore had emulsifier concentrations of 1.0, 1.2, and 1.6 wt% for the systems stabilized with caseinate, Tween 80, and saponin, respectively. For the emulsions prepared with excess gum arabic, an emulsifier concentration of 15 wt % was used because higher values led to emulsion instability. Blank emulsions were prepared having the same composition as the