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Insight into natural biopolymer-emulsified solid lipid nanoparticles for encapsulation of curcumin: Effect of loading methods

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ABSTRACT

Encapsulation of lipophilic bioactives into solid lipid nanoparticles (SLNs) has been a promising approach to incorporate them into functional foods with attempt to improve bioavailability. Nevertheless, how these bioactives should be loaded into the lipid core have never been systematically studied before. Thus, in the present study, biopolymer-emulsified SLNs were prepared using a recently developed synthetic surfactant-free technique, and four different loading methods were tested for their efficacy to encapsulate curcumin into SLNs. Sodium caseinate (NaCas) and pectin were used as natural emulsifier and stabilizer, respectively, to prepare food-grade SLNs using stearic acid. Four loading methods varied in the use of organic solvent, and the order of critical steps including addition of curcumin and solid lipids, deprotonation of NaCas at pH 12, as well as pectin adsorption at pH 4. The resulting four types of curcumin-loaded SLNs were subject to comprehensive characterization, such as measurement of particle size, polydispersibility, zeta potential, stability test in simulated gastrointestinal (GI) fluids, antioxidant activities of encapsulated curcumin, as well as morphological observation under transmission electron microscopy. Nano spray drying technology was then exploited to obtain ultrafine powders from colloidal SLNs and their redispersibility in water was also evaluated. Our results suggested that solubilization of curcumin in deprotonated NaCas was a better approach than using organic solvent which resulted in large and aggregated SLNs. Furthermore, mixing curcumin with deprotonated NaCas and then adding melted lipid and pectin at pH 12 before emulsification were the two critical steps in fabricating uniform and small SLNs that were GI-stable and re-dispersible in water after spray drying. This study provides insight into the preparation of natural biopolymer-emulsified SLNs as a potential food-grade oral delivery system for lipophilic bioactives.

1. Introduction

Lipid-based nanodelivery system is a major type of colloidal delivery systems that are applicable to the development of nanotechnology-enabled functional foods. Comparing with protein- and carbohydrate-based nanodelivery systems, lipid-based formulations, such as nanoemulsions, solid lipid nanoparticles (SLNs) and nanostructured lipid carriers, have the potential for scale-up production at the industrial level (Fathi, Mozafari, & Mohebbi, 2012; Weiss et al., 2008). This is largely attributed to the easy fabrication procedures under mild conditions for production of lipid nanoparticles, which possess high acceptability, non-toxicity and excellent compatibility for their use in food products. Particularly, the hydrophobic nature of solid lipids provides high affinity to the lipophilic nutrients and thus exceptional encapsulation efficiency and slow release profile (Aditya & Ko, 2015).

Although SLNs have promising features for use in food products, their practical applications in the food industry have not yet realized and several long-standing challenges are to be overcome (Müller, Mäder, & Gohla, 2000; Weiss et al., 2008). First, the use of organic solvent is a critical issue limiting its applications in food products, while removing process is tedious and may devastate nanostructures of lipid core, resulting in the formation of large aggregates. For instance, ethanol and isobutanol were used as solvent and co-surfactant in the preparation of SLNs for encapsulation of anthocyanin (Ravanfar, Tamaddon, Niakousari, & Moein, 2016). Second, the successful preparation of SLNs and their dispersion in aqueous phase are often contingent upon the use of high

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concentration of synthetic surfactants, which pose potential risk of toxicity in final formulations. It has been reported that up to 45% tween 80 was needed in the SLNs formulation to achieve a desirable effect on improving oral bioavailability of curcumin (Kakkar, Singh, Singla, & Kaur, 2011). Therefore, extensive efforts have been currently prioritized among food and nutrition scientists to address the above two major challenges for realizing the practical applications of SLNs in food products.

Our recent studies have demonstrated the feasibility to prepare SLNs using natural food biopolymers as stabilizers and emulsifiers, completely avoiding the use of synthetic surfactants (Wang et al., 2017; Xue, Wang, Hu, Zhou, & Luo, 2017). In particular, sodium caseinate (NaCas) from milk protein and pectin from Citrus peel are the two natural food biopolymers, and their interactions under acidic pH condition have been successfully exploited as a novel approach to prepare and stabilize SLNs in our previous studies mentioned above. In principle, adjusting pH of NaCas and pectin mixture to slightly acidic condition induced strong electrostatic interactions between two polymers and thus created a coating network on the surface of SLNs, followed by strengthening the hydrophobic interactions between the formed polymeric coating and emulsified lipid droplets upon heating. The subsequent cooling process solidifies the lipid droplets and their complexation with polymeric coating, resulting in the formation of a compact structure.

As a potential oral delivery systems for food applications, however, the loading and encapsulation capability of as-developed NaCas and pectin-emulsified SLNs has not yet been investigated. Herein, the present study aims to explore the effects of different loading techniques on the encapsulation of curcumin into such SLNs. In particular, four different loading techniques were developed and tested, differing in the use of organic solvent and the order of critical steps including addition of curcumin and solid lipids, deprotonation of NaCas at pH 12, as well as pectin adsorption at pH 4. The resultant curcumin-loaded SLNs were fully characterized to optimize the loading process. The particulate characteristics, including particle size, polydispersity index, and zeta potential, were compared and the colloidal stability in simulated gastrointestinal tract was also assessed to evaluate their suitability as a potential oral delivery system in food products. Furthermore, two in-vitro antioxidant assays were studied to elucidate the effect of loading techniques on the antioxidant activity of encapsulated curcumin.

2. Materials and methods

2.1. Materials

Stearic acid, pepsin, pancreatin, ethanol, hydrochloric, sodium hydroxide, vitamin C, and iron (III) chloride were purchased form Fisher Scientific Co., (Norcross, GA, USA). AAPH [2,20-azobis-(2-amidinopropane) dihydrochloride], ABTS [2,20-azino-bis(3-ethylbenzthiazoline6-sulfonic acid) diammonium salt], potassium ferricyanide, disodium hydrogen phosphate, sodium dihydrogen phosphate, and trichloroacetic acid were obtained from Sigma-Aldrich. Sodium caseinate (NaCas) from bovine milk, and pectin (galacturonic acid content≥74%) from citrus peel were also purchased from Sigma-Aldrich Corp (St. Louis, MO, USA). All reagents and solvents were analytical grade and used with further purification.

2.2. Preparation of biopolymer-emulsified SLNs

Pectin and NaCas were respectively dissolved in water at 5 mg/mL as stock solutions, and after complete hydration both solutions were adjusted to pH 7.0 using 1.0 M NaOH and stored at 4 °C prior to use. In general, the biopolymer-emulsified SLNs were prepared by a hot emulsification method as reported in our previous studies (Wang, Ma, Lei, & Luo, 2016; Wang, Xue, Hu, Zhou, & Luo, 2017), but without use of organic solvents or synthetic surfactants. Briefly, equal volume (5 mL) of diluted solutions of pectin (2 mg/mL) and NaCas (2 mg/mL) were mixed together under mild stirring and heated to 75 °C. Then, 10 mg of solid lipid (stearic acid powder) was added to the above pre-heated pectin/NaCas mixture, followed by 5 min vigorous stirring and 3 min sonication using a probe sonicator (Misonix Sonicator® 3000, USA) at 20 kHz, consecutively. After cooling down in ice bath, samples were adjusted to pH 4 and re-heated to 70 °C for 30 min to induce electrostatic and hydrophobic interactions between NaCas and pectin to form biopolymeric coating network on the surface of SLNs.

2.3. Loading curcumin into SLNs

In this study, four loading methods with 3 different curcumin loading concentrations (1, 2, and 4% weight ratio to solid lipid) for each method were investigated. For Method 1 (M1), curcumin was pre-dissolved in ethanol solution and then added into lipid-NaCas/pectin mixture at 75 °C, followed by sonication, cooling, pH adjustment and re-heating processes, consecutively. For Method 2 (M2), all procedures were the same to M1 except that curcumin powder was used, instead of pre-dissolved in ethanol. For Method 3 (M3), curcumin powder was added into the NaCas solution which was pre-adjusted to pH 12 under stirring for 30 min, and then the curcumin-NaCas mixture was neutralized to pH 7 using 1 M HCl. Then, pre-heated pectin solution was added, followed by sonication, solid lipid addition, sonication, cooling, pH adjustment and re-heating processes. For Method 4 (M4), curcumin powder was added into NaCas solution which was pre-adjusted to pH 12 under stirring for 30 min, and then the above mixture was heated to 75 °C, followed by consecutive addition of solid lipid powder and pre-heated pectin. Subsequently, the mixture was neutralized to pH 7, followed by sonication, cooling and re-heating processes. To better illustrate the four loading methods, detail information of procedures was illustrated in Fig. 1.

2.4. Characterization of SLNs

Dynamic light scattering (DLS) technique was employed to determine particle size, count rate and polydispersity index (PDI) using Zetasizer Nano ZS (Malvern Instruments Ltd, Worcestershire, UK), while electrophoretic mobility was measured by the same instrument to calculate zeta potential. Prior to each measurement, samples were diluted 10 times to avoid multiple scattering effect.

2.5. Evaluation of gastrointestinal stability

Freshly prepared curcumin-loaded SLNs prepared by four loading methods were subject to physical stability measurement in simulated gastric and intestinal fluids, based on recently published literature (Xue et al., 2017). Briefly, SLNs were diluted 10 times with either simulated gastric fluid (SGF), containing 2.0 mg/mL sodium chloride and 2.917 mg/mL hydrochloric acid (adjusted to pH 2 or pH 4 with 1 mg/mL pepsin, mimicking fasting and fed state condition, respectively), or simulated intestinal fluid (SIF, containing 0.616 mg/mL sodium hydroxide and 6.8 mg/mL potassium phosphate monobasic) at pH 7 with 10 mg/mL pancreatin, followed by incubation in 37 °C water bath for 2 and 4 h, respectively. After incubation, particle size, PDI and zeta potential were determined by DLS, as described in Section 2.4.