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Polymeric micelles of octenylsuccinated corn dextrin as vehicles to solubilize curcumin

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ABSTRACT

Hydrophobized polysaccharides are promising substrates for the micellar entrapment of lipophilic food ingredients. In this study, we investigated the solubilization of curcumin with octenylsuccinated corn dextrin micelles. A Box-Behnken design was used to determine the dependence of the apparent solubility of curcumin on the operation parameter (the stirrer input power, *IP*) and the structural parameters (molecular weight, M_w, and degree of substitution, DS) of octenylsuccinated corn dextrin micelles. Additionally, the properties of curcumin-loaded octenylsuccinated corn dextrin micelles were characterized. The maximal apparent solubility of curcumin (4.44 μg/mL) encountered with an intermediate *IP* (4.0 W), M_w (10.4×10^4 Da) and DS (0.0302). The curcumin-loaded octenylsuccinated corn dextrin micelles were spherical in shape with a mean diameter of 247 nm. Lyophilization and reconstitution showed insignificant effect on polydispersity index and ζ-potential of the curcumin-loaded micelles ($p > 0.05$). Curcumin entrapped in octenylsuccinated corn dextrin micelles was in an amorphous state, as revealed by Fourier transform infrared spectroscopy, differential scanning calorimetry, and X-ray diffraction. The results suggested that octenylsuccinated corn dextrin micelles displayed encouraging capacities as a nano-carrier for solubility enhancement of curcumin.

1. Introduction

Curcumin is a natural phenolic food additive (E 100) obtained from the rhizomes of the plant turmeric (*Curcuma longa*). In addition to its traditional use as a spice and food colorant in Asian countries, curcumin has been demonstrated as a health-promoting agent. Curcumin has exhibited a broad spectrum of beneficial properties, including anti-inflammatory (Chainani-Wu, 2003), antimicrobial (De et al., 2009), anticancer (Gong et al., 2013; Nair, Thulasidasan, Deepa, Anto, & Kumar, 2012) and antioxidant (Gazal et al., 2014) activities. However, curcumin's extremely low water solubility (11 ng/mL, 25 °C) severely hinders its application in food and related products (Kaminaga et al., 2003). This characteristic is also responsible for curcumin's low bioavailability, which mitigates its therapeutic effects. To enhance the solubilization of curcumin, several carriers or vehicles including micelles (Yoncheva et al., 2015), emulsions (Sari et al., 2015), nanocomposite (Li, Shin, Lee, Chen, & Park, 2016), liposomes (Jin, Lu, & Jiang, 2016), conjugates (Sarika, James, Kumar, Raj, & Kumary, 2015), polymeric nanoparticles (Nair et al., 2012), and lipid nanoparticles (Righeschi et al., 2016) have been investigated.

Polymeric micelles have been extensively applied for the solubilization of hydrophobic bioactive molecules. In comparison with the micelles of small molecular surfactants, polymeric micelles formed by polymeric surfactants have a relatively low critical aggregation concentration (CAC), which implies that the polymeric micelles are more resistant upon dilution when incorporated into the food matrix or other biological fluids (Lu & Park, 2013). Polymeric micelles from pharmaceutically acceptable amphiphilic block copolymers such as poly(ethylene oxide)-*b*-poly(ε-caprolactone) (Ma et al., 2008), methoxypoly(ethylene glycol)-*b*-poly(ε-caprolactone-co-*p*-dioxanone) (Song, Shen et al., 2011), poly (D, L-lactide-co-glycolide)-*b*-poly(ethylene glycol)-*b*-poly(D, L-lactide-co-glycolide) (Song, Feng et al., 2011), and monomethyl poly(ethylene glycol)-poly(ε-caprolactone) (Gong et al., 2013) have been widely used as vehicles for curcumin solubilization. These micelles demonstrated curcumin loading capacity in the range of 6–15%, increasing the apparent solubility of curcumin thousands-fold (Gong et al.,

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2013; Song, Feng et al., 2011). Moreover, polymeric micelles from amphiphilic block copolymers were applied for sustained and targeted delivery of curcumin (Song, Shen et al., 2011; Yoncheva et al., 2015).

Although micellar entrapment by the block copolymers is one of the promising approaches to enhance curcumin's water solubility, these block copolymers are always not acceptable in the food industry. Alternatively, octenylsuccinylated starches are a low-cost food-grade amphiphilic polysaccharide that has been granted GRAS status. In fact, they are already used as an encapsulating and emulsifying agent in various food products. Yu and Huang (2010) reported that curcumin can be easily entrapped into micelles formed by a hydrophobically modified starch synthesized with waxy maize and *n*-octenyl succinic anhydride (Hi-Cap 100, National Starch and Chemical Company, Bridgewater, NJ, USA), which resulted in approximately 1670-fold enhancement of curcumin solubility in water.

Previously, we have developed polymeric micelles based on hydrophobized polysaccharides, including octenylsuccinated oat β-glucan and fatty acid oat β-glucan esters (Chen, Liu, Ye, & Zhao, 2014; Liu et al., 2014; Liu, Li, Ma, Chen, & Zhao, 2013). These polymeric micelles had relatively low CAC values and showed good solubilizing capacity toward curcumin (Chen et al., 2014; Liu et al., 2014). We also synthesized an octenylsuccinated corn dextrin (OSCD), which formed spherical self-assemblies in water (Lei, Liu, Ye, Chen, & Zhao, 2014). Structurally, OSCD highly resembles octenylsuccinated starch, but has a remarkably low CAC (0.052 ± 0.002 mg/mL) compared to Hi-Cap 100 (Lei et al., 2014; Yu & Huang, 2010). We hypothesize that OCSD micelle is able to encapsulate curcumin by solid dispersion method without using any surfactants or organic solvent. In this study, we applied response surface methodology to investigate the structural characteristics of OCSD (the degree of substitution, DS, and molecular weight, M_w) and the operation parameter (the stirrer input power, *IP*) on the apparent solubility of curcumin in OCSD micelles. The properties of curcumin-loaded OCSD micelles were characterized.

2. Experimental

2.1. Materials

Curcumin (bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione, 98% purity) was supplied by Adamas Reagent Co., Ltd. (Shanghai, China). Commercial food grade corn starch was supplied by Jiaxian Food Industry Co., Ltd (Chongqing, China). 2-Octen-1-ylsuccinic anhydride (Product No. 416487) was purchased from Sigma Chemical Co. (St. Louis, MO, USA). All other chemicals were of analytical grade and used as received.

2.2. Synthesis of octenylsuccinated corn dextrin

Octenylsuccinated corn dextrin (OSCD), in which octenylsuccinyl groups are covalently attached to the dextrin chains through ester linkages (Fig. 1), have been synthesized according to a method previously applied in our laboratory (Lei et al., 2014). Detailed information on reaction conditions and degree of substitution (DS) of OSCD samples is shown in Table 1.

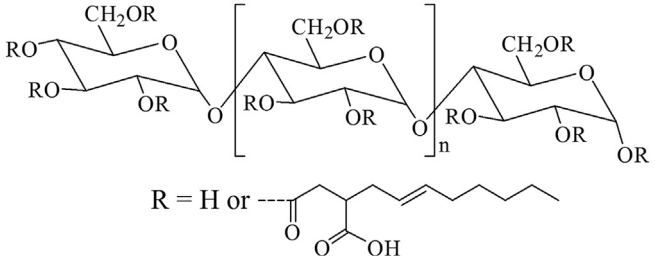

Fig. 1. Structural formula of octenylsuccinated corn dextrin.

2.3. Loading curcumin into octenylsuccinated corn dextrin micelles

Precisely weighed freeze-dried OSCD powder was dissolved in distilled water at room temperature to make a 10 mg/mL of aqueous solution. Excess amount of curcumin was mixed with the 10 mg/mL of OSCD micelles and homogenized at 10 000*g* for 1 min with a homogenizer (IKA T18 basic, IKA-Werke GmbH & Co., Staufen, Germany). In a dark room, the resultant homogenate was continuously stirred under different *IP* values (Table 3) at 25 °C for 24 h to complete the transfer of curcumin into OSCD micelles. Free curcumin was removed by high-speed centrifugation (15 000*g* for 30 min) and filtered through a 0.45 μm filter.

2.4. Experimental design

Response surface methodology (RSM) based on the Box-Behnken design was adopted to observe the effects of *IP* of operation as well as M_w and DS of OSCD on the apparent solubility of curcumin ([CUR]) of OSCD micelles. A three-level, three-variable design was used in the present study. The three independent variables are *IP* (X_1), M_w (X_2), and DS (X_3); [CUR] was used as the dependent variable response. The factorial design consisted of 12 factorial points and 5 central points. The coded and uncoded independent variables used in the RSM design are listed in Table 3. To complete this experiment totally, nine OSCDs should be synthesized (Table 1). Theoretically, as a requirement of the experiment design, nine OSCDs could be evenly divided into three groups, and OSCDs in the same group possess identical DS but the differentiated M_w. However, it is an impossible task to obtain an identical DS for corn dextrin with different M_w. Therefore, three OSCDs with different M_w and insignificantly differentiated DS were grouped in the present study (Table 2). All trials were performed in triplicate. Design-Expert software version 7.0 (STAT-EASE Inc., Minneapolis, MN, USA) was used to generate the experimental designs, statistical analysis, and regression model. A second-order polynomial equation was used to express the predicted responses of [CUR] as functions of the independent variables, as shown in the following equation:

$$Y_i = a_0 + a_1X_1 + a_2X_2 + a_3X_3 + a_{12}X_1X_2 + a_{13}X_1X_3 + a_{23}X_2X_3 + a_{11}X_1^2 + a_{22}X_2^2 + a_{33}X_3^2 \quad (1)$$

where X_i represents the independent variables; a_0 is a constant; and a_i, a_{ii}, and a_{ij} are the linear, quadratic, and interactive coefficients, respectively.

2.5. Quantification of curcumin from octenylsuccinated corn dextrin micelles

The apparent solubility of curcumin ([CUR], μg/mL) is defined as the amount of curcumin (μg) in 1 mL of curcumin-loaded OSCD micelle solution. To determine [CUR] values, curcumin was solvent-extracted from the samples (Yu & Huang, 2010). Equal volume of chloroform was vortexed with the curcumin-loaded OSCD micelle solution for 10 min and then stirred on a magnetic stirrer overnight. The suspension was centrifuged (10 000 *g* for 20 min) for complete phase separation, then the chloroform phase was diluted 10 times