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Research Article

Facile Synthesis of Curcumin-Loaded Starch-Maleate Nanoparticles

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We have demonstrated the loading of curcumin onto starch maleate (SM) under mild conditions by mixing dissolved curcumin and SM nanoparticles separately in absolute ethanol and ethanol/aqueous (40 : 60 v/v), respectively. Curcumin-loaded starch-maleate (CurSM) nanoparticles were subsequently precipitated from a homogeneous mixture of these solutions in absolute ethanol based on the solvent exchange method. TEM analysis indicated that the diameters of CurSM nanoparticles were ranged between 30 nm and 110 nm with a mean diameter of 50 nm. The curcumin loading capacity of SM as a function of loading duration was investigated using the UV-visible spectrophotometer. The loading of curcumin onto SM increased rapidly initially with loading duration, and the curcumin loading capacity of 15 mg/g was reached within 12 hours. CurSM nanoparticles exhibited substantially higher water solubility of 6.0×10^{-2} mg/mL which is about 300 times higher than that of pure curcumin. With enhanced water solubility and bioaccessibility of curcumin, the potential utility of CurSM nanoparticles in various biomedical applications is therefore envisaged.

1. Introduction

Curcumin, a non-toxic bioactive component of turmeric even at high dosage [1], has attracted considerable attention especially for its pharmacological activities such as anti-carcinogenic [2, 3], anti-inflammatory [4, 5], and antioxidant [6]. However, the utility of curcumin in clinical development and applications is limited by its low water solubility and poor bioavailability [7]. The solubility of curcumin in water is reported to be 1.99×10^{-4} mg/mL [8]. However, the solubility of curcumin is reported to be pH dependence, and it is soluble in both strong acids [9] and dilute alkali of pH 11 [10].

Any drawback due to poor water solubility of hydrophobic bioactive agents such as curcumin could be circumvented via the development of nanoparticle-based drug delivery systems that are dispersible in aqueous media. Intense research efforts have therefore been focused on developing curcumin-loaded polymeric nanoparticles for enhancing the water solubility of curcumin. Anand and co-researchers [11] have reported the synthesis of curcumin-loaded PLGA nanoparticles with enhanced water solubility. Although curcumin is pharmacologically safe for human beings, the efficacy of curcumin-loaded synthetic polymers has remained uncertain.

Various attempts have been made to synthesize polysaccharide-loaded curcumin nanoparticles. Being a type of polyphenolic molecule, curcumin could interact strongly with glucan molecule through hydrogen bonding. Such non-covalent interactions of curcumin might play a decisive role in its mechanism of actions during various pharmacological activities. Cyclodextrin, a type of polysaccharide, is known to form inclusion complexes with curcumin [12–14]. Kaminaga et al. [15] reported the conjugation of glucose molecules with curcumin molecules to form water soluble prodrugs. Gupta et al. [16] reported the encapsulation of curcumin with silk fibroin and chitosan to form curcumin-based nanoparticles using the blending method. Such encapsulation of curcumin by natural biopolymers could eliminate tissue toxicity.

In this paper, we have reported a facile synthesis approach for the preparation of water soluble curcumin-loaded starch-maleate (CurSM) nanoparticles by loading curcumin onto highly water-soluble starch-maleate monoester. The chemical structure, morphology, and mean size of CurSM nanoparticles were characterized by both FTIR and TEM.

The curcumin loading capacity of SM nanoparticles and the resulting water solubility of CurSM nanoparticles were determined by the UV-visible spectrophotometer.

2. Materials and Method

2.1. Materials. Native sago starch powder was obtained from local grocery store. Sodium hydroxide (CAS No. 1310-73-2) was supplied by Mallinckrodt. Curcumin (1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione) (CAS No. 458-37-7) and maleic anhydride (CAS No. 108-31-6) were purchased from Merck. Absolute ethanol (CAS No. 64-17-5) was purchased from Hamburg. All chemicals were used without further purification. Ultrapure water (18.2 MΩ) was used in all syntheses.

2.2. Method

2.2.1. Preparation of Curcumin-Loaded Starch-Maleate (CurSM) Nanoparticles. The preparation of starch-maleate monoester (SM) was described elsewhere with some modifications [17]. In this study, SM was prepared by dispersing 16.2 g native sago starch in 10 mL of ultrapure water and 25 mL of 2.0 M NaOH. This was followed by adding 15.8 g solid maleic anhydride and heating at 80°C for 4 hours. SM sample was then precipitated in absolute ethanol. The loading of curcumin onto SM was carried out by mixing 1% curcumin solution in absolute ethanol with SM monoester dissolved in an ethanol/aqueous (40 : 60 v/v) mixture. Typically, 0.1 g of SM was first dissolved in 10 mL of 40% ethanol, and 10 mL of 1% curcumin solution in absolute ethanol was added. The resulting clear yellow solution was stirred continuously at a constant stirring rate for various predetermined time intervals (3, 4, 5, 6, 8, 12, and 16 hrs) at 50–60°C. Absolute ethanol was then added into the SM and curcumin solution mixture. The yellow precipitate formed was rinsed several times with absolute ethanol to remove any free curcumin adhered onto surfaces of CurSM nanoparticles. Since free curcumin was completely soluble in absolute ethanol, it was removed during repeated rinsing with absolute ethanol. To ensure complete removal of free curcumin adhered onto surfaces of CurSM nanoparticles, the concentration of curcumin in the supernatant was determined by measuring the absorbance at 420 nm using a UV-vis spectrophotometer (Perkin Elmer/Lambda 25) against a standard curcumin solution. The yellow CurSM precipitate was dried in a conventional oven at 60°C for 24 hours. CurSM nanoparticles were subsequently prepared by the solvent exchange method as described previously [18]. Typically, 0.1 g of CurSM powder was dissolved in 10 mL ultrapure water and then added dropwise into 40 mL of absolute ethanol. The resulting nanoparticles in suspension were sonicated and centrifuged 3 times and washed with absolute ethanol to remove any free curcumin on the surface of CurSM nanoparticles. The purified CurSM nanoparticles were dried in an oven at 60°C for 24 hours.

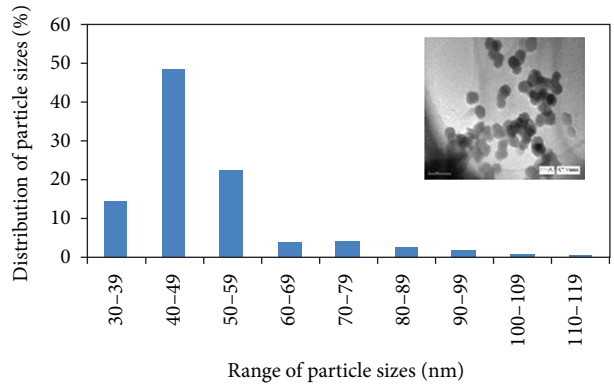

Figure 1: Particle size distribution of CurSM nanoparticles prepared with a loading duration of 14 hours at 50–60°C. Inset shows the TEM micrograph of CurSM nanoparticles precipitated in absolute ethanol.

2.2.2. Curcumin Loading Capacity of Starch Maleate (SM). The total loading of curcumin onto SM was determined by dissolving CurSM nanoparticles in ultrapure water. 0.020 g of CurSM nanoparticles was dissolved in ultrapure water to form 5 mL of CurSM solution at ambient temperature. The amount of curcumin adsorbed was then determined using a UV-vis spectrophotometer (Perkin Elmer/Lambda 25) at the wavelength of 350 nm.

2.2.3. Confocal Laser Scanning Microscope Analysis. A small drop of the CurSM dispersion in absolute ethanol was mounted on a slide and visualized using a confocal laser scanning microscope (CLSM) (LSM 410, Carl Zeiss, USA).

2.2.4. Transmission Electron Microscopy (TEM) Analysis. Dispersed CurSM samples in absolute ethanol were dropped onto formvar-coated copper grids and characterized using a transmission electron microscope (TEM) (JEOL Model JEM 1010). The mean size of CurSM nanoparticles was determined by measuring randomly 50 nanoparticles as observed in the TEM micrographs.

2.2.5. Fourier Transformed Infrared Spectrometry (FTIR) Analysis. Fourier transformed infrared spectrometry (FTIR) spectra of CurSM, SM as well as curcumin samples pelleted with potassium bromide (KBr) were generated using a fourier transformed infrared spectrometer (SHIMADZU Model FTIR-8201PC) within the wave number range of 4000 and 400 cm^{-1}.

3. Results and Discussion

3.1. Preparation of CurSM Nanoparticles. Curcumin was successfully loaded onto starch-maleate monoester (SM) and subsequently formed discrete CurSM nanoparticles of irregular distorted spherical shape via the nanoprecipitation process in absolute ethanol. Figure 1 shows the particle size distribution of CurSM nanoparticles with size ranging between 30 and 120 nm and a mean size of 50 ± 12 nm.

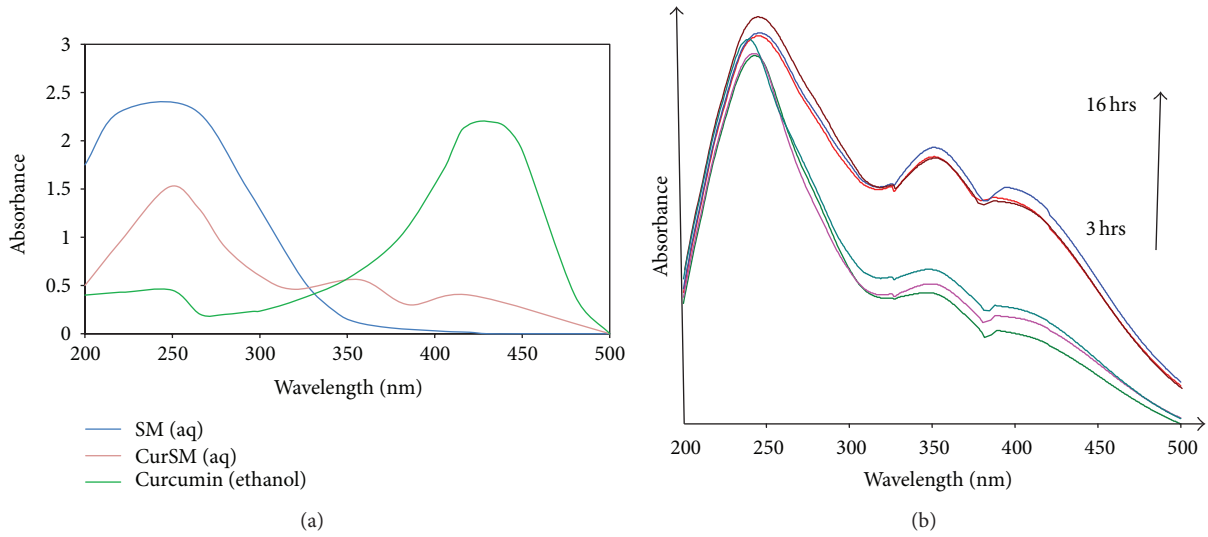

FIGURE 2: UV-visible spectra of (a) SM (aqueous), CurSM (aqueous), and curcumin (ethanolic) solutions, and (b) 0.4% (w/v) aqueous solutions of CurSM samples prepared with different loading durations (3–16 hours).

The TEM micrograph (inset of Figure 1) shows CurSM nanoparticles of distorted spherical shape which could be attributed to their high sensitivity to gelation in the presence of water. Nevertheless, the preparation method used in the present study appeared to afford good particle size control of CurSM nanoparticles.

3.2. UV-Visible Spectra of CurSM. Figure 2(a) shows the superimposed UV-visible spectra of SM and CurSM aqueous solutions and ethanolic solution of free curcumin within the scanning wavelength range of 200 and 500 nm. SM aqueous solution and curcumin ethanolic solution exhibited prominent absorption peaks at 250 nm and 420 nm, respectively, in consonance with respective reported results [18, 19]. The absorption peak of SM at the wavelength of 250 nm was attributed to the π-π^* transition of unsaturated groups of maleate moiety within the SM molecules [18]. Free curcumin in absolute ethanol was reported to exhibit an intense, round-shaped absorption band centered at 420 nm in the visible region [19]. This could be attributed to its extended aromatic system with electronic dipole that allowed the π-π^* type of excitation. Upon light absorption, a π electron was excited from the ground state to the first excited state and oscillated from one end of the chromophore to the other. Ferrari et al. [20] reported that curcumin in physiological pH range undergoes tautomeric equilibrium which is highly solvent dependent. Curcumin exhibited an absorption peak in the UV-vis spectrum at around 320 nm, which was attributed to its predominant diketo form. However, the predominant keto-enol tautomer in aprotic/apolar solvent exhibited an absorption peak at 420 nm [20]. Henceforth, the loading efficiency and capacity of curcumin onto starch maleate could be substantially influenced by the tautomeric equilibrium of curcumin under prevailing experimental conditions. CurSM aqueous solution showed three prominent absorption peaks at 250 nm, 350 nm, and 420 nm which could be attributed to

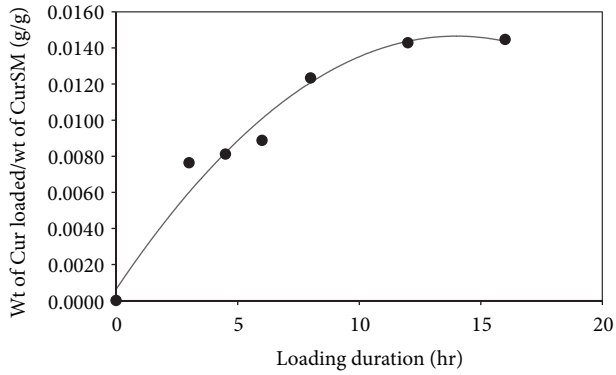

FIGURE 3: The loading profile of curcumin onto starch maleate as a function of loading duration (0.4% of CurSM solution).

SM, curcumin loaded within SM, and free curcumin, respectively. Intensities of these absorption peaks should correspond to their relative abundance within the CurSM sample. However, contradictory results had also been reported for free curcumin solution which exhibited a prominent peak at 350 nm and was attributed to the n-π^* transition of the feruloyl unit of curcumin [21, 22].

The UV-visible spectra of CurSM aqueous solutions with samples prepared at different curcumin loading durations within the wavelength range of 200 and 400 nm were shown in Figure 2(b). The different intensities of two prominent peaks at wavelengths of 250 nm and 350 nm indicated the relative abundance of SM moiety and curcumin component, respectively, present in each CurSM sample. Very similar intensities of absorption peaks at 250 nm indicated that the concentration of SM moieties had remained almost constant throughout the curcumin loading durations. It is noteworthy that the absorption peak of curcumin within CurSM samples appeared to have blue shifted toward the near-ultraviolet (354–366 nm) region. Such shift could be attributed to the

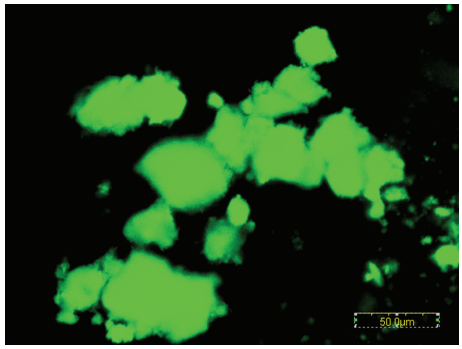

Figure 4: Aconfocal laser scanning micrograph of curcumin loaded starch maleate (CurSM) dispersed in absolute ethanol.

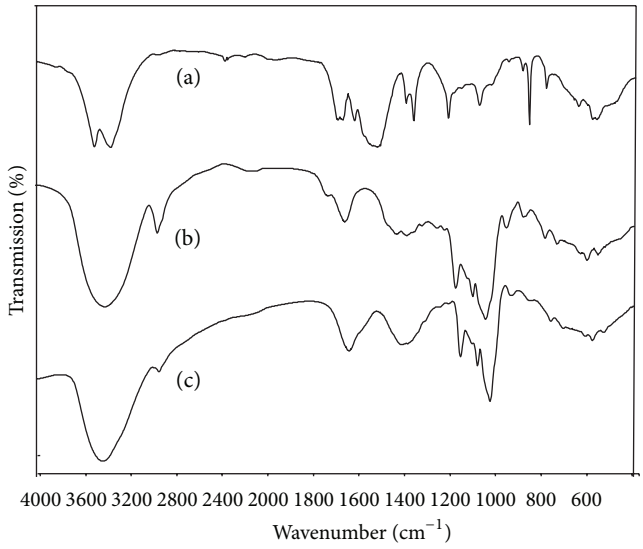

Figure 5: FTIR spectra of (a) curcumin, (b) starch maleate (SM), and (c) curcum loaded starch-maleate (CurSM).

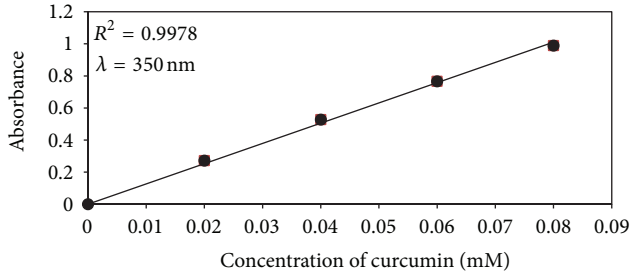

Figure 6: Absorbance of alkaline curcumin aqueous solution at the wavelength of 350 nm within the concentration range of 0–0.08 Mm.

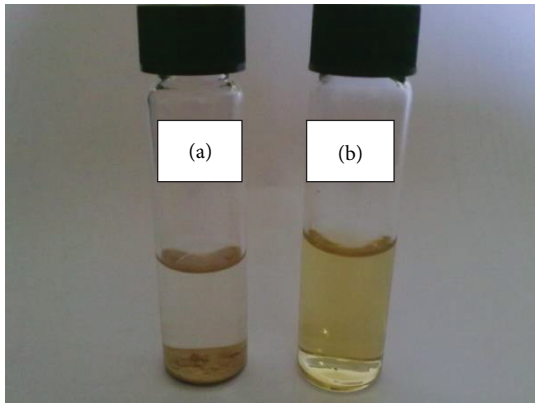

Figure 7: Photographs of CurSM samples in (a) absolute ethanol and (b) water.

electronic dipole n-π^* transition of the carbonyl group of curcumin, which might normally be obscured by the strong masking effect of neighboring absorption bands [6]. We therefore speculated that SM molecules in aqueous solution would interact readily with hydroxyl groups of curcumin molecules through hydrogen bonding. Such interactions would sterically prevent these molecules from adopting the planar geometry and hence gave rise to the observed shift of absorption peaks toward the near ultraviolet (354–366 nm) region.

Figure 3 shows the loading profile of curcumin onto SM as a function of loading duration which was monitored based on the absorbance measured at the wavelength of 350 nm. A low temperature of 50–60°C was employed during the loading process in order to reduce degradation of polysaccharide chains of the SM sample. The loading of curcumin onto SM was observed to increase more rapidly initially with increasing loading durations, and the loading capacity of about 15 mg/g was reached within 12 hours.

Since curcumin produced natural fluorescent in the visible green spectrum, no further labeling of curcumin was necessary when it was being examined using a confocal laser scanning microscope (CLSM). Prior to CLSM analysis, the CurSM sample was rinsed three times with absolute ethanol in order to remove any free curcumin adhered onto the sample surface. As shown in Figure 4, the bright green patches and spots indicated the presence of curcumin within the CurSM sample.

3.3. FTIR Analysis. Figure 5 shows FTIR spectra of curcumin, SM, and CurSM samples. The FTIR analysis was carried out to confirm the loading of curcumin onto starch-maleate molecules. Curcumin was observed to exhibit several dominant peaks which were attributed to functional groups such as O–H (3508 cm^{-1}), C=O, C=C (1626 cm^{-1}), and aromatic C=C (1602 cm^{-1}), whereas SM showed the characteristic absorption peak at around 1700 cm^{-1} which was attributed to the carbonyl group. However, the characterization of CurSM samples using FTIR spectroscopy had been hindered by interfering vibrations of starch molecules at very similar wave numbers [23]. Furthermore, the conventionally high relative molecular mass of starch molecules could lead to relatively weak absorption peaks of curcumin as compared to those of starch molecules. Besides, the amorphous nature of CurSM samples had resulted in absorption peaks being less sharp and less intense than those peaks observed in the

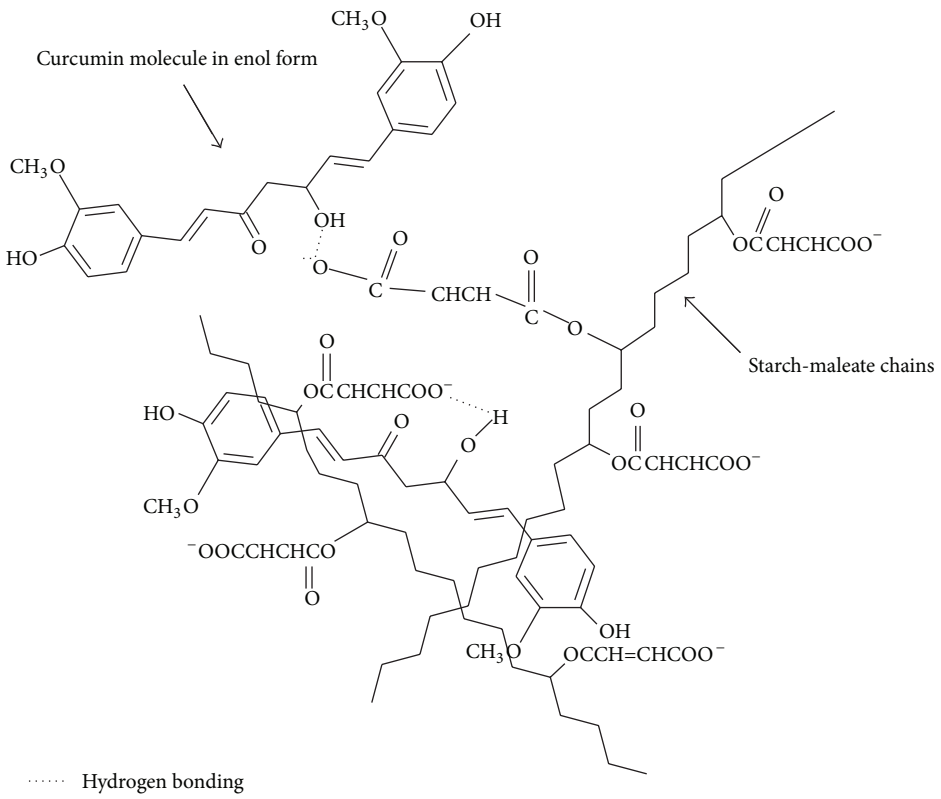

Figure 8: Schematic representation of interactions between curcumin molecules and starch-maleate molecules via hydrogen bonding.

spectrum of curcumin. As such, the presence of curcumin moiety within the CurSM samples could not be readily discernable in the FTIR spectra.

3.4. Solubility of Curcumin and CurSM Nanoparticles. Curcumin is extremely insoluble in water, and this feature has restricted its clinical applications. However, concerted research efforts had been focused on synthesizing water soluble curcumin derivatives due to their superior antioxidant activity against *in vitro* human cancers. Curcumin and curcuminoid derivatives displayed absorption peaks in the ultraviolet and visible regions. The absorbance of alkaline curcumin aqueous solution measured at the wavelength of 350 nm was observed to increase linearly ($R^2 = 0.9978$) with curcumin concentration of up to 0.08 mM at 25°C (Figure 6). According to some authors [24] symmetrical curcumin molecule absorbed at a wavelength of 360 nm. A shoulder peak was observed at 360 nm for curcumin in basic media [25]. This showed that the solubility of curcumin in an alkaline aqueous medium could be 0.08 mM or higher.

As shown in Figure 7, CurSM nanoparticles were visibly insoluble in absolute ethanol but readily soluble in water to produce a clear yellowish brown solution. Being a polyphenolic type of molecule, curcumin molecule was able to interact strongly with biomacromolecules through hydrogen bonding as illustrated in Figure 8. Curcumin had been shown to interact with biomacromolecules such as protein, cyclodextrin, and phospholipid [11]. As reported by several authors [14], curcumin could form water soluble complex with cyclodextrin. Hydrogen bonding interactions had been reported to occur between curcumin and other molecules such as phosphatidylcholine [26]. The aqueous solubility of CurSM nanoparticles is calculated to be 6.0×10^{-2} mg/mL which is 300x higher than that of free curcumin (1.99×10^{-4} mg/mL [8]). The loading of curcumin onto water soluble starch-maleate could have resulted in substantial changes in the microenvironment of curcumin molecules due to extensive hydrogen bonding interactions between curcumin and SM molecules. Such interactions could have contributed towards enhanced solubility of curcumin in water since SM by itself was highly soluble in water.

The enhanced solubility of CurSM nanoparticles in aqueous medium could also be attributed to their nano-sized dimensions and associated large specific surface area, as well as the highly hydrophilic nature of starch-maleate molecules. Besides, traces of NaOH could be entrapped within CurSM samples despite our efforts to remove them by reprecipitating these CurSM samples in absolute ethanol for several times. Such traces of entrapped NaOH could have also contributed towards the observed higher aqueous solubility of CurSM samples.

4. Conclusion

The present study has demonstrated a facile approach for loading of curcumin onto starch-maleate monoester. Besides,

water soluble curcumin-loaded starch-maleate (CurSM) nanoparticles of spherical shape were synthesized in aqueous-based system through controlled nanoprecipitation of CurSM solution in absolute ethanol. The total loading of curcumin onto SM nanoparticles could be modulated by varying the duration of loading. Due to their biocompatibility, nontoxic nature, and enhanced water solubility, the potential utility of CurSM nanoparticles in biomedical applications is therefore envisaged.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

Acknowledgments

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