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To cite this article: Katherine *et al* 2018 *IOP Conf. Ser.: Mater. Sci. Eng.* **299** 012038

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Determination of process parameters for curcumin – dextrose cocrystallization

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Abstract. Curcumin is a polyphenol that could act as anti-oxidant and anti – inflammation agent. It is usually isolated from rhizome plants such as turmeric and temulawak. Despite its many favorable properties, curcumin is practically insoluble in water, thus limiting its application. In the present investigation, variables affecting preparation of curcumin-dextrose cocrystal were examined with the aim to increase the solubility of curcumin. The effect of different processing conditions, such as water to dextrose ratio, final heating temperature and water bath temperature to the formation of cocrystal, were studied and the yield and solubility of curcumin – dextrose cocrystal products were analyzed. The morphology of the cocrystals were also analyzed using SEM and fluorescence microscopy. Curcumin – dextrose cocrystals showed a significant increase in solubility up to 25 mg curcumin per mL water compared to pure curcumin.

Keywords: *cocrystallization, curcumin, dextrose*

1. Introduction

Curcumin ((1,7-Bis-(4-hydroxy-3-methoxyphenyl)-hepta-1,6-diene-3dione) is a polyphenol extracted from turmeric (*Curcuma longa*) and temulawak (*Curcuma xanthorrhiza*). It is widely used as natural food colorants. In addition, curcumin has demonstrated several therapeutic effects in the treatment of cancer, HIV infection, and antioxidant [1]. However, the low solubility of curcumin in water limits its usage and bioavailability. In order to overcome this limitation, various methods has been suggested, such as using nanocarrier [2], high pressure homogenization [3] and cocrystallization with pyrogallol and recorcinol [4].

Cocrystallization is one interesting alternative method to improve curcumin solubility as the method is simple, shows high yield and six times increase in solubility [4]. However, the cofomer used previously was considered toxic. Therefore, there is a need to find a safer cofomer. In this study, dextrose was chosen as a cofomer because it is a generally considered as safe (GRAS) compound and easily obtained. In addition, a simple method of cocrystallization employing solubilization of cofomer by heating followed by cooling to achieve supersaturation was introduced. While the method has not been used for curcumin, the method has been successfully employed in encapsulation of cardamom oleoresin [5], yerba mate[6], honey [7], and orange peel oil [8] to stabilize the active ingredients.



2. Material and methods

2.1. Material

Curcumin and ethanol were obtained from Merck (Jakarta). Dextrose monohydrate was purchased from Bratachem (Bandung). All chemicals were of analytical grade.

2.2. Methods

2.2.1. Determination of dextrose recrystallization process parameters

Preparation of supersaturated dextrose solution is the initial step in the recrystallization process. Important factors investigated in this step were water to dextrose ratio, final heating and cooling temperature. Water of different volumes was added to 15 g of dextrose to obtain ratio of water to dextrose as shown in Table 1. The mixture was then heated with a laboratory hot-plate while stirring with magnetic stirrer. The temperature of the mixture was monitored continuously during heating process. The heating process was stopped when the desired final temperature was achieved (Table 1). Afterwards, the solution was removed from hot-plate and cooled inside a water bath. In order to control the cooling rate, the temperature of water bath was set according to Table 1. Once the temperature reached 50°C, ethanol was added while the solution was continuously stirred. The solution was further transferred into a silicone mold and cooled inside a water bath until cocrystals were formed. Water and ethanol were finally removed from the cocrystals by drying in oven for 24 hours at 40°C.

Table 1 Recrystallization process parameters

Mass ratio of water to dextrose	0:15	1:15	2:15	3:15
Final heating temperature (°C)	90	100	110	120
Water bath temperature (°C)	30	35	40	-

2.2.2. Cocrystallization of curcumin with dextrose

Cocrystallization was performed by mixing ethanolic solution with sugar solution. 15 g of dextrose was dissolved in water (weight ratio of 1:15). The dextrose solution is then heated while stirring until 100 °C. Once the desired temperature was achieved, the dextrose solution was cooled while continuously stirred in a preheated water bath (35 °C). until its temperature decreased to 50°C. Curcumin solution (0.125 mg curcumin/mL ethanol) was subsequently added while stirring to minimize heat-induced curcumin degradation. The mixture was then poured into silicon mold and, placed in water bath to further decrease the temperature of the solution. The cocrystals formed upon cooling were transferred into evaporation cups, and finally dried in a vacuum oven for 24 hours at 40°C to evaporate the remaining solvent. Dried cocrystal products were stored in tightly closed container to protect them from moisture and light.

2.2.3. Morphology analysis

The morphology of curcumin dextrose cocrystal was analyzed using Scanning Electron Microscopy (JEOL JSM 6510 LA, Japan). Prior to analysis, the samples were spread on the surface of double – face carbon tape and coated with gold. In addition, bright-field and fluorescence microscopy images of the cocrystals were captured using fluorescence microscope type Nikon Eclipse E800 at 400x magnification.

2.2.4. Curcumin content determination

Curcumin content was analyzed by using UV – vis spectrophotometer (Genesys 20, Spectronic) at the peak absorbance wavelength for curcumin, i.e. 430 nm. At this wavelength, dextrose posed no interference to curcumin, because dextrose absorption occurred at lower wavelength (260 - 270 nm)[9]. The ethanol – water mixture is chosen as solvent for its ability to dissolve curcumin at higher concentration. To determine curcumin content in the cocrystal, 300 mg cocrystal was dissolved in a known amount of water. A 10 mL aliquot was taken and centrifuged for five minutes at 6000 rpm, and 8 mL of ethanol was further added to 2 mL of the obtained supernatant. The absorbance of obtained mixture was then measured with the spectrophotometer, and curcumin concentration was determined using a calibration curve built from measuring the absorbances of series of curcumin in 80% ethanol-water standard solutions. The yield of curcumin is defined as the actual amount of curcumin in the cocrystal divided by the initial amount of curcumin added.

2.2.5. Solubility of curcumin – dextrose cocrystal

The solubility of curcumin in cocrystal in water was measured by adding amount of cocrystal to 10 mL water while stirring until it reached saturation. After centrifugation at 6000 rpm, 2 mL of the supernatant was mixed with 8 mL of ethanol. The solution was then analyzed for its curcumin content with Vis spectrophotometer.

3. Result and Discussion

3.1. Dextrose recrystallization process parameters

Prior to cocrystallization of curcumin – dextrose, the crystallization process parameters were investigated to ensure consistent crystal formation. Crystallization process is affected by temperature at which the crystallization is initiated, water content and cooling rate [7].

Water content affects the formation of crystals. In cocrystallization of curcumin - dextrose, low water content is desired due to low solubility of pure curcumin in water. In addition, high water content decelerates crystal formation [10]. However, absence of water necessitates higher heating temperature to completely melt dextrose. Moreover, high temperature usage should be avoided due to tendency of dextrose to caramelize. By fixing final heating temperature to 100°C, it was found that mass ratio of water to dextrose mass is optimum at 1:15. Crystals were formed within 7 minutes. At mass ratio of water to dextrose 0:15, dextrose could not completely melt. Meanwhile, both mass ratio of water to dextrose 2:15 and 3:15 yielded highly viscous dextrose solution which could only crystallized after more than 24 hours.

The final heating temperature was varied from 90°C to 120°C. Not all dextrose particles were dissolved at 90°C. Meanwhile, when heated to 110°C and above, the color of dextrose solution changed to slightly yellow, which indicated the formation of caramel. At the optimum temperature of 100°C, dextrose was dissolved into transparent colorless liquid.

Solution supersaturation significantly determines the development of nucleation and crystal growth. One method to control supersaturation is by controlling cooling rate. A fast cooling rate favors nucleation over crystal growth as it increases supersaturation level, which leads to formation of large population of small size crystals. On the other hand, low cooling rate favors crystal growth over nucleation, resulting in formation of small population of large crystals [11]. In addition, cooling rate needs to be investigated to determine the time needed for addition of curcumin solution and homogenization of the mixture. Fast cooling rate will result in formation of cocrystals with inconsistent curcumin content. In this work, cooling rate was controlled by immersing dextrose solution container in the water bath. Setting the water bath to 30°C accelerated crystal formation, which caused crystals

formation prior to homogenization. Therefore, minimum water bath temperature for cocrystallization was set at 35°C.

3.2. Curcumin – dextrose cocrystal characterization

Figure 1 shows the morphology of curcumin – dextrose cocrystal. SEM image (Figure 1a.) shows that the cocrystal is a mixture of flakes and smaller irregular particles, with length of flakes about 10 μm and length to width ratio of 5. The size of the small irregular particles is about 1 μm . Some of the flake particles formed aggregates with the smaller particles trapped inside or attached to the surface of the flakes.

SEM image is incapable of differentiating dextrose from curcumin. In order to locate curcumin, fluorescence microscope was employed. Figure 1b shows the cocrystal under bright – field microscope while Figure 1c shows the same sample under fluorescent microscope. Under the bright-field microscope, the cocrystals appeared as an aggregate with dark color. Using mercury – vapor lamp as light source, some part of the crystals appeared bright green. The green color came from curcumin as curcumin has fluorescence property [12]. The image indicates that distribution of curcumin in cocrystal is not uniform.

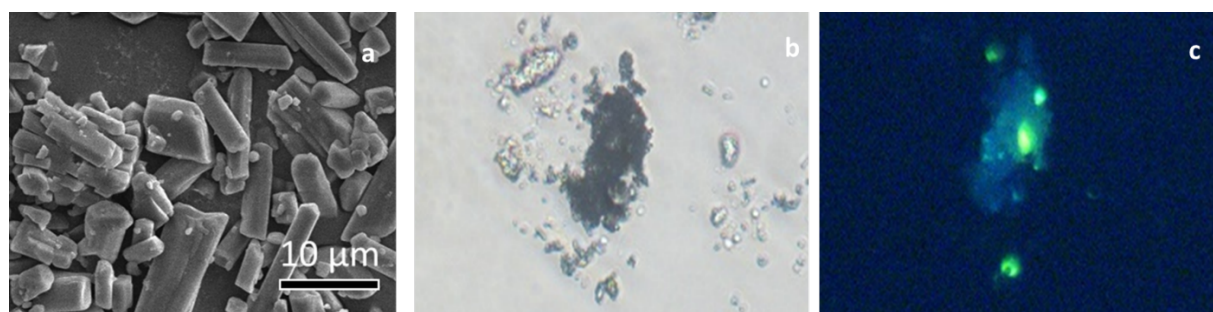


Figure 1. Curcumin – dextrose cocrystal observed using (a). SEM at 1500 x magnification, (b) bright-field microscope at 400x magnification and (c) fluorescence microscope at 400x magnification

The yield of curcumin was up to 90% in cocrystal. Pure curcumin (Figure 2a) could not be detected by spectrophotometer as it was insoluble. According to a study, the water solubility of curcumin was reported to be 0.6 $\mu\text{g}/\text{ml}$ [13]. Initial trial to dissolve the crystal in water showed that the cocrystal is highly soluble (Figure 2c). Quantitative analysis indicates that the solubility of the cocrystals containing 0.2% curcumin is about 25 mg curcumin per mL of water. This shows a significant increase compared to pure curcumin. The curcumin dispersed in dextrose solution was also insoluble, which can be shown in Figure 2b. This confirms that curcumin solubility is not caused by presence of dextrose.

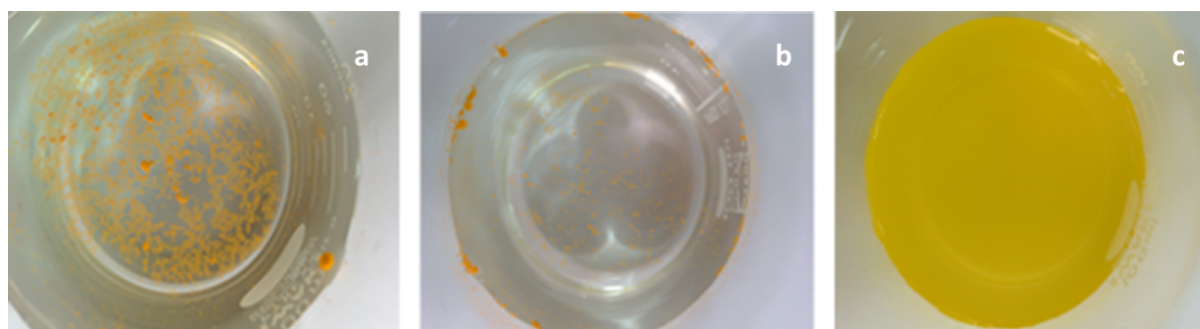


Figure 2. (a) curcumin dispersed in water, (b) curcumin dispersed in dextrose solution, (c) curcumin – dextrose cocrystal dispersed in water

4. Conclusion

This work demonstrates the preparation of highly – soluble curcumin – dextrose cocrystal. Parameters such as mass ratio of water to dextrose, final heating temperature and cooling temperature were identified. The optimum parameters for curcumin – dextrose cocrystallization were mass ratio of water to dextrose 1:15, final heating temperature of 100°C, and water bath temperature of 35°C. The curcumin – dextrose cocrystals consisted of a mixture of flakes and small irregular particles in which curcumin was distributed unevenly. The increase solubility of curcumin shows a promising potential of curcumin – dextrose cocrystals. Investigation on stability of curcumin – dextrose cocrystals, effect of curcumin concentration in the cocrystallization, and also the curcumin – dextrose interaction is currently carried out and will be reported in forthcoming papers .

5. Acknowledgement

This work was funded by Hibah Monodisplin Universitas Katolik Parahyangan. The authors would like to thank Universitas Katolik Parahyangan for the grant received. The author would also like to thank Dr. Solmaz Aslanzadeh for proofreading the manuscript.

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