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The Potency of Inulin to Increase Curcumin Aqueous Solubility as a Co-Processing Material with *Curcuma longa* in Solid Dispersion Approach

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ABSTRACT
Curcumin, an identical compound of *Curcuma longa* extract, shows limited bioavailability due to its lipophilicity. Inulin of degree of polymerization (DP) of 11 is a carbohydrate member that can potentially increase aqueous solubility and dissolve lipophilic compounds. This study aimed to investigate inulin DP 11 at various drug loads of curcumin on the solubility and dissolution of curcumin. The inulin and *C. longa* extract were co-processed using a solid dispersion (SD) technology on a spray dryer and were analyzed for curcumin solubility as well as dissolution. The drug content (drug load) of SD formulations was prepared at 10%-30% w/w. As the control, the corresponding drug load was designed without applying the SD technology, called physical mixture (PM) formulations. The results suggest that employing the SD technique, inulin DP 11 co-processed with curcumin enhances the aqueous solubility of curcumin compared to the corresponding PM formulations. The dissolution as analyzed for dissolution efficiency (DE) of the SD samples was enhanced by factors 1.7, 2.9, and 3.3 for the drug load of 10%, 20%, and 30% w/w, respectively. To conclude, inulin DP 11 is favorable to enhance curcumin aqueous solubility and dissolution using am SD platform.

Keywords: *Curcuminoids, Dissolution, Extracts, Spray drying.*

1. INTRODUCTION

Turmeric (*C. longa*) rhizomes contain curcuminoids, which are natural polyphenolic compounds. Curcuminoids are comprised of curcumin, dimethoxy curcumin, and bis-dimethoxy curcumin, all of which are yellow-colored molecules, with curcumin being the most abundant component in this combination [1]. Curcumin's medicinal potential has been demonstrated in numerous research, particularly those relating to its anti-oxidant and anti-inflammatory characteristics [2]. Curcumin has poor absorption and inconsistent bioavailability upon oral dosing despite its countless favorable pharmacological properties, limiting its potential as a pharmaceutical agent [3]. Curcumin, a lipophilic molecule with an estimated log P 3.2, has a minimal water solubility (11 ng/mL) [4], allowing it to easily precipitate in the gastrointestinal milieu's aqueous environment. As a result, improving curcumin solubility is critical to ensuring an adequate amount of bioavailable curcumin.

Co-processing material using solid dispersions (SD) approach has been gaining interest during the last half-century to improve the aqueous solubility and bioavailability of lipophilic drugs. SD consists of a lipophilic drug(s) incorporated into a hydrophilic carrier (matrix), e.g., by fusion or solvent evaporation method, providing an improved release profile [5]. Polyvinylpyrrolidone or polyethylene glycol was the most popular matrix material used in SD applications study. We recently used an oligosaccharide called inulin DP 11. Inulin is a fructan family of indigestible carbohydrates, a water-soluble storage polysaccharide. Inulin has been demonstrated in multiple studies to have various health benefits, including feeding healthy gut flora, lowering the risk of gastroenteritis and other digestive problems, and boosting the immune system [6]. As a hydrophilic compound with its high-water

solubility, inulin can affect in helping wetting of lipophilic compounds to increase the water solubility. We propose using inulin to be applied in an SD approach to enhance the aqueous solubility of curcumin. This study aimed to examine the potential use of inulin to improve curcumin aqueous solubility and dissolution using a co-processing way with the SD approach.

2. MATERIALS AND METHODS

Curcumin as a standard compound (>98% purity) was obtained from Sigma-Aldrich (St. Louis, USA). High curcuminoids content of *C. longa* extract of > 97%) was given by PT Phytochemindo Reksa, Bogor, Indonesia. Inulin of degree polymerization of 11 (Inulin DP 11) was kindly provided by Dr. W.L.J Hinrichs from the Department of Pharmaceutical Technology and Bio-pharmacy, University of Groningen, the Netherlands. Methanol, sodium lauryl sulfate (SLS), and sodium dihydrogen phosphate (NaH_2PO_4) were purchased from Merck (Darmstadt, Germany). Purified water was supplied using Milli-Q water equipment.

2.1. Preparation of the SDs formulation

Inulin-based SDs were prepared at 10%, 20%, 30% w/w drug load of curcumin. In brief, ethanolic solution *C. longa* extract was prepared at 10.0 mg/mL. Inulin DP 11 of 50 mg/mL was dissolved in pre-heated water under magnetic stirring for 15 minutes. Curcumin-ethanolic and inulin DP 11 aqueous solutions were mixed under magnetic stirring [7], followed by 40 minutes of ultrasonication in a sonicated bath. The solution mixtures were prepared as follows; 10%, 20%, 30% w/w drug load were prepared from the mix of 10/18, 20/16, 30/14 volume ratios of extract and inulin solutions. The mixed solutions were spray-dried at a flow rate of 6 mL/min via a two-way channel with a nozzle diameter of 0.7 mm on a Büchi B-290 micro spray dryer fitted with a B-295 dehumidifier (Büchi, Flawil, Switzerland). The solvent was evaporated at 105°C inlet temperature, 100 percent aspiration, 6 mL/min feeding rate, and 500 Ln/h atomization pressure. The output temperature was found to be between 60-65 degrees Celsius. The yield was calculated, and the SD products were dried and stored in a desiccator until the sample was characterized. Drug load evaluation of the solid dispersion samples was conducted a UV-Vis spectrophotometry (Shimadzu 1800, Shimadzu Co. Ltd., Kyoto, Japan) at 421 nm. Curcumin content was quantified based on a calibration sample in which it demonstrates the linear equation of y = 0.146x + 0.0193 at the correlation coefficient of 0.9966.

2.2. Preparation of PM sample

PM samples were used as the control experiment. In brief, *C. longa* extract and inulin DP 11 at the corresponding drug load were gently mixed on a mortar and sieved using a 60-mesh size.

2.3. Solubility evaluation

The SD and PM formulations were subjected to a solubility test. An excess amount of powder was poured into an aqueous sodium phosphate buffer of pH 6.0 at the buffer concentration of 20 mM. Sampling was conducted within 48 hours. Curcumin concentrations of the samples were determined using a double beam UV-VIS spectrophotometer at λ of 429 nm (Shimadzu 1800, Shimadzu Co. Ltd., Kyoto, Japan) based on the linear equation of y = 0.1279x + 0. 009 and correlation coefficient (r) of 0.9974.

2.4. Dissolution study

Curcumin release was studied on a USP type 2 SOTAX AT7 dissolution tester. The solid dispersion samples and the corresponding physical mixture formulations were filled into capsules of 00 size. The tablets were placed in a dissolution vessel that contained a dissolution medium of 900 mL of 0.5% SLS in 20 mM of sodium phosphate buffer of pH 6.0. The dissolution test was operated at 37±0.5°C and agitation of 75 rpm for 120 minutes. At predetermined time intervals, a 5.0 mL volume was sampled and replaced by a fresh dissolution medium to maintain the sink condition during the study. Curcumin concentration in the dissolution samples was quantified using the validated UV-VIS spectrophotometry method at λ of 429 nm (Shimadzu 1800, Shimadzu Co. Ltd., Kyoto, Japan). The concentration was obtained using the linear equation of y= 0.12790x + 0. 0090 and correlation coefficient (r) of 0.99740. Furthermore, the dissolution profile obtained in 120 minutes study was analyzed using a Dissolution Efficiency (DE) approach based on Equation 1.

$$DE_t = \frac{\int_{t1}^{t2} y.dt}{y_{100}.t}) \times 100\% \quad (1)$$

DE	:	The dissolution efficiency at a pre-determined time
y	:	The area under the curve (AUC) of the dissolved drug at the time
y100.t	:	the area of a rectangle assumed for total drug (100%) dissolved at a particular time

2.5. Statistical analysis

Statistical calculations were conducted on the solubility and dissolution tests on the SD and PM formulations. The dissolution test performed statistical analysis to see the difference in dissolution profile (DE_{120}) between the SD and the PM and between the SD

formula. The test carried out is the normality test using the Shapiro-Wilk test. If the data is normally distributed, then it is tested its significance with the T-test. If the data is not normal, the test is carried out with the Mann-Whitney test and Kruskal-Wallis test for data more than two on a 95% confidence level.

3. RESULTS AND DISCUSSION

Co-processed material consisting of *C. longa* extract and inulin DP 11 using the SD approach on the spray drying method yields 73.31%, 69.99%, and 67.86% w/w for the drug load of 10% w/w, 20% w/w, and 30% w/w, respectively. The results show the higher the proportion of inulin DP11 over the *C. longa*, the more the yield is obtained.

The drug load of the SD samples was found at a recovery of 94.43±0.16% w/w; 96.05±0.16 %w/w; and 92.78±0.32% w/w. The recovery results show satisfaction. According to the USP monograph on curcuminoids dosage form, the active ingredient content in dosage form products should be between 90.0 and 110.0 percent. As a result, the curcumin detected in the co-processed material of *C. longa* – inulin DP 11 in the SD formulation meets the USP monography's product standard [8].

The solubility test aims to see the solubility of the SD compared to the PM formulations at the corresponding drug load. A solubility test was carried out by dissolving the powder at an excess amount in a specific buffer volume. Due to the stability concern of curcumin, in that curcumin was most stable at pH 6.0 [4], a phosphate buffer solution (pH 6.0) was used as the media to dissolve the PM and SD powder.

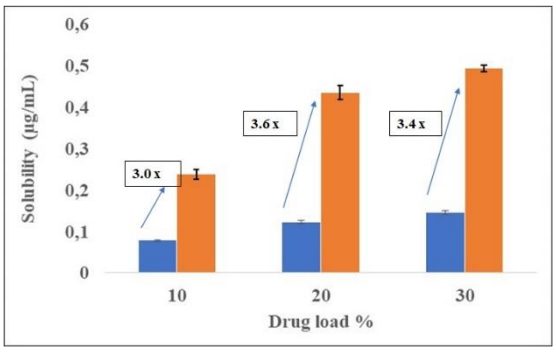

Figure1. Solubility of curcumin in water. Blue color: PM and orange color: co-processed SD. The experiment was replicated with the N=3

Figure 1 shows the solubility test for curcumin in the SD and the PM formulations prepared at various drug loads. After 48 hours, the amount of aqueous soluble curcumin was found of 0.078 µg/mL, 0.123 µg/mL, and 0.146 µg/mL in the PM formulations of 10%, 20%, and 30% drug load, respectively. The aqueous solubility of curcumin demonstrated by the SD was significantly higher than the PM formulations; the amount of curcumin dissolved in the SD increased to 0.234 µg/mL, 0.435 µg/mL, and 0.493 µg/mL in the accordingly drug load. Furthermore, using the solid dispersions approach, co-processing material of C. longa with inulin DP 11dramatically enhanced the curcumin solubility by a factor of 3.0, 3.6, and 3.4 for 10%, 20%, and 30% drug load ($p<0.05$). From this data, it can be concluded that co-processing *C. longa* extract with inulin DP 11 using solid dispersions approach to magnify the aqueous solubility of curcumin.

Dissolution studies demonstrated the release profile of curcumin from the inulin DP 11 based SD formulations and provided a comparison with the corresponding PM formulations. The dissolution profiles were analyzed for the dissolution efficiency (DE) values to compare dissolution profiles obtained in 120 minutes dissolution study. The DE values are presented in Figure 2.

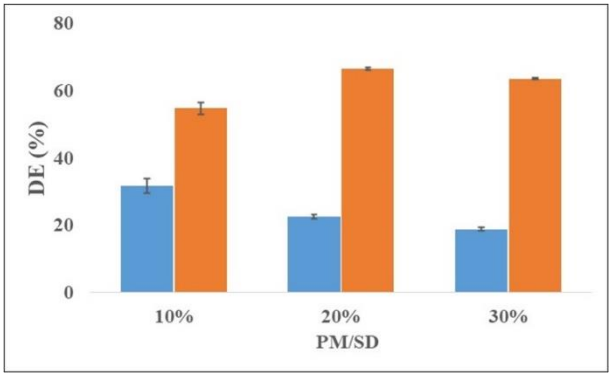

Figure 2. Dissolution efficiency (DE) of the PM and SD formulas. PM: blue color; SD: orange color. The experiment was replicated with the N=3

The DE values found in the PM formulation were 31.57%, 22.52%, and 18.80% for the drug load of 10%, 20%, and 30%, respectively. In accordingly drug load, the SD formulations demonstrated higher DE than the PM formulations, which are 54.71%, 66.53%, and 63.54%. The incorporation of C. longa demonstrated the enhancement in curcumin release into solid dispersion formulation in which the dissolution increased by factors 1.73, 2.89, 3.41 for the drug load of 10%, 20%, and 30%, respectively. Others found an increase in curcumin dissolution in co-processed formulation with inulin. Fares and Salem [9] reported the formation of the curcumin-inulin conjugate facilitated the enhancement of curcumin dissolution. Another study found that the use of inulin DP23 increased the dissolution of a lipophilic compound of an HIV viral inhibitor, TMC240; 80% of the drug was released during 30 minutes dissolution study [10].

These data prove that co-processing *C. longa* and inulin DP 11 using solid dispersions approach increased the dissolution efficiency of curcumin at all drug loads used in this experiment.

Inulin DP 11 enhances curcumin aqueous solubility and dissolution by processing it with solid dispersions approach using spray drying method. Inulin DP 11 is applicable in processing *C. longa* extract with an improved dissolution of curcumin. The increment in curcumin dissolution of curcumin by incorporating C. longa extracts into inulin-based solid dispersions reaches up to three times as compared to the physical mixture formulation.

AUTHORS CONTRIBUTIONS

Dewi Setyaningsih: Conceived and designed the experiments; analyzed and interpreted the data; contributed reagents, materials, analysis tools, or data; Wrote the paper. Elizabeth Vianita Kurniawan: Performed the experiments. Yustina Sri Hartini: Analyzed and interpreted the data.

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REFERENCES

[1] K.M. Nelson, J. L. Dahlin, J. Bisson, J. Graham, J.F. Pauli, M.A. Walters, The essential medicinal chemistry of curcumin, J Med Chem, vol. 60, 2017, pp. 1620-1637.

[2] R. Tabrizi, S. Vakili, M. Akbari, N. Mirhosseini, K.B. Lankarani, M. Rahimi, M. Mobini, S. Jafarnejad, Z. Vahedpoor, Z. Asemi, The effects of curcumin-containing supplements on biomarkers of inflammation and oxidative stress: a systematic review and meta-analysis of randomized controlled trials, Phytother. Res., vol. 33, 2019, pp. 253-262.

[3] S.C. Gupta, S. Patchva, B.B. Aggarwal, Therapeutic roles of curcumin: lessons learned from clinical trials, AAPS J, vol. 15, 2012, pp. 195-218.

[4] Y.J. Wang, M.H. Pan, A.L. Cheng, L.I. Lin, Y.S. Ho, C.Y. Hsieh, J.K. Lin, Stability of curcumin in . B solutions and characterization of its degradation products, J Pharm Biomed Anal, vol. 15, 1997, pp. 1867-1876. DOI: 10.1016/S0731-7085(96)02024-9.

[5] W.L. Chiou, S. Riegelman, Preparation and dissolution characteristics of several fast-release solid dispersions of griseofulvin, Journal of Pharmaceutical Sciences, vol. 58, 1969, pp. 1505-1510.

[6] M. Shoaib, A. Shehzad, M. Omar, A. Rakha, H. Raza, H.R. Sharif, A. Shakeel, A. Ansari, S. Niazi, Inulin: properties, health benefits, and food applications, Carbohydrate Polymers, vol. 147, 2016, pp. 444-454.

[7] D. Van Drooge, W.L.J. Hincrichs, K.A.M Wegman, M.R. Visser, A.C. Eissens, H.W. Frijlink, Solid dispersions based on inulin for the stabilization and formulation of Δ9-tetrahydrocannabinol, European Journal of Pharmaceutical Sciences, vol. 21, 2004, pp. 511-518.

[8] USP, Dietary supplements monographs curcuminoids, in USP Pharmacists' Pharmacopeia., U.S Pharmacopeia: Rockville, 2019, pp. 1-7.

[9] M.M. Fares, M.T.S. Salem, Dissolution enhancement of curcumin via curcumin–prebiotic inulin nanoparticles, Drug Development and Industrial Pharmacy, vol. 41, 2015, pp. 1785-1792.

[10] M.R. Visser, L. Baert, G. van't Klooster, L. Schueller, M. Geldof, I. Vanwelkenhuysen, H. De Kock, S. De Meyer, H.W. Frijlink, J. Rosier, Inulin solid dispersion technology to improve the absorption of the BCS Class IV drug TMC240, European Journal of Pharmaceutics and Biopharmaceutics, vol. 74, 2010, pp. 233-238.