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Physical Interaction between Curcumin and Paracetamol in the Binary Mixture and Its Impact on the Solubility of Curcumin

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A B S T R A C T

Curcumin, found in turmeric (*Curcuma longa* L.), is a pharmacologically active component with hepatoprotective properties. In addition to alleviating pain, the synergistic effects of paracetamol protect the liver from harm. Oral solid dose formulations of curcumin have low bioavailability due to its low solubility. This study aims to characterize the physical interactions that occur in the binary mixture of curcumin and paracetamol and to determine its impact on the solubility of curcumin. The curcumin-paracetamol binary mixture with a 1:1 stoichiometric ratio was prepared by a wet grinding method with the addition of a small amount of ethanol. The characterization of the physical interactions in the wet milling result was carried out using a powder X-ray diffractometer (PXRD) and a differential scanning calorimeter (DSC). Evaluation of physicochemical properties was carried out by testing its solubility in water and its dissolution rate in 40% v/v ethanol. The PXRD pattern of the curcumin-paracetamol milling result did not show any new peaks that were different from the typical peaks of the two components (curcumin form I and paracetamol form 1). The thermogram DSC of the binary mixture curcumin-paracetamol (1:1) only showed one wide endothermic transition at 151.2°C which is below the melting point of curcumin and paracetamol which is thought to be the melting point of the eutectic mixture of curcumin-paracetamol (1:1). The solubility of curcumin from the curcumin-paracetamol (1:1) milled binary mixture was 8.3-folds higher than that of pure curcumin. The dissolution rate of curcumin from the wet milling of the curcumin-paracetamol binary mixture (1:1) was also faster than that of pure curcumin. The research results can be concluded that wet milling of the binary mixture of curcumin-paracetamol (1:1) with a little ethanol shows a physical interaction with the formation of a simple eutectic mixture between the two substances which has an impact on increasing the solubility and dissolution rate of curcumin.

1. Introduction

Curcumin is a natural polyphenol obtained from the isolation of the turmeric plant (Curcuma longa) or other rhizomes with various efficacy, such as anti-inflammatory (Chainani-Wu, 2003; Peng *et al.*, 2021), hepatoprotective (Kyung *et al.*, 2018; Ibrahim *et al.*, 2020), and antimicrobial (Adamczak, Ożarowski and Karpiński, 2020; Hussain *et al.*, 2022). The ability of curcumin as a hepatoprotector is reported to be able to prevent liver damage induced by paracetamol when given concurrently (Sayed and El-Kordy, 2014). In addition, the combination of curcumin and paracetamol given orally can work synergistically in reducing pain in mice induced by acetic acid (Utomo, Cicih and Nurdian, 2017). Therefore, the combination of curcumin and paracetamol has high potency when administered in oral pharmaceutical dosage forms, such as capsules or tablets.

One of the main problems of orally administered drugs is low solubility which adversely affects bioavailability. Curcumin has low solubility which causes poor bioavailability during oral administration. Some efforts to increase the solubility of curcumin have been carried out by reducing particle size through the manufacture of nanocrystals (Rachmawati *et al.*, 2013; Oshi *et al.*, 2020) and solid dispersions (Gangurde *et al.*, 2015). In addition to the manufacture of nanocrystals and solid dispersions, efforts to increase the solubility of curcumin are also carried out by mixing curcumin with low molecular weight excipients that interact physically to form co-crystal through hydrogen bonds, including with ascorbic acid (Pantwalawalkar *et al.*, 2021), resveratrol (Dal Magro *et al.*, 2021), n-acetylcysteine (Paulazzi *et al.*, 2022).

Physical interactions that occur in binary mixtures between pharmaceutical active ingredient and expand or with another active pharmaceutical ingredient often do not show interactions to form co-crystal, but can prevent crystallization of another substance and show lower melting point than the two components known as a simple eutectic mixture (Bazzo, Pezzini and Stulzer, 2020). The simple eutectic mixture is also able to increase the solubility of active pharmaceutical ingredients, such as glimepiride-arginine (Park *et al.*, 2020), caffeine-meloxicam (Alshaikh, Essa and El Maghraby, 2019), and hydrochlorothiazide-atenolol (Haneef and Chadha, 2017).

The advantages of the curcumin and paracetamol combination make these two active pharmaceutical ingredients have a great potential to be mixed in solid pharmaceutical dosage forms. However, until now there has been no study on the physical interactions that occur between the mixture of curcumin and paracetamol. Therefore, this study aims to characterize the physical interactions that occur in the binary mixture between curcumin and paracetamol and determine its impact on the solubility of curcumin.

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2. Research Methods

Instruments and materials

The instruments used in this research were spectrophotometer UV-visible (Shimadzu UV-1801), dissolution tester (Veego scientific), differential scanning calorimeter (Shimadzu DSC-60 Plus), X-ray Diffractometer (Philips PW1710), polarized microscope (Olympus BX-53), and orbital shaker (IKA® KS 260 basic). Curcumin was obtained from Merck Indonesia with a purity of more than 95%, while paracetamol was obtained from PT. Brataco Chemical, Indonesia with purity above 99%. Ethanol was also purchased from Merck Indonesia.

Experimental

1. Identification of polymorphic forms of curcumin and paracetamol raw materials by powder X-ray diffraction method

   An amount of approximately 500 mg each of curcumin and paracetamol was placed in an aluminum holder and the surface was leveled. The samples were scanned with an X-ray diffractometer at a speed of 2°/min at an angle range of 2° 5-45°. The voltage of the device is conditioned at 40kV with a current of 30mA. The diffractograms of the two raw materials are compared with the diffractograms from the literature to determine the shape of the polymorphs.

2. Preparation of an equimolar ratio of the curcumin-paracetamol binary mixture by wet grinding method

   An amount of 184 mg curcumin (0.5 mmol) was ground together with 75 mg paracetamol (0.5 mmol) in a mortar. The grinding process was done by adding a few drops of ethanol. The milled result was dried and stored in a desiccator before being characterized and evaluated.

3. Characterization of the curcumin-paracetamol binary mixture by powder X-ray diffractometer

   Determination of the powder X-ray diffraction (PXRD) pattern of curcumin-paracetamol (1:1) milling result was performed according to the measurement procedures and conditions as in the identification of polymorphic forms of curcumin and paracetamol raw materials.

4. Characterization of the curcumin-paracetamol binary mixture by differential scanning calorimeter (DSC)

   Thermal analysis of DSC was performed on curcumin, paracetamol, and curcumin-paracetamol (1:1) milling result. An amount of 3-5 mg of each compound was placed in an aluminum crucible pan, placed in the apparatus, and heated in the range of 30-200°C. The instrument was operated at 10°C/min of heating rate.

5. Phase solubility test of curcumin in paracetamol solution

   Each 10 mL of a paracetamol solution in water with a concentration of 10, 20, 40, 60, 70, and 80 mM was put into the vial. Fifty mg of curcumin was added to each vial and shaken in an orbital shaker for 24 hours. After completion of shaking, the liquid in the vial was filtered and the filtrate was analyzed using a UV-Visible spectrophotometer at 426 nm to determine the dissolved curcumin.

6. Solubility test

   The solubility of curcumin was performed by a shake-flask method (Murdande *et al.*, 2011). A total of 50 mg of curcumin was put into a 10 ml vial filled with water. The vial was shaken in an orbital shaker at 250 rotations per minute for one day. After completion, the liquid in the vial was filtered and the filtrate was analyzed using a UV-visible spectrophotometer at 426 nm.

7. Dissolution test

   The dissolution test conditions were conducted based on the tests that had been carried out by previous researchers (Sanphui *et al.*, 2011). The amount of milled curcumin-paracetamol used for the dissolution test was equivalent to 40 mg of curcumin. The test used a type 2 dissolution apparatus (paddle) with 100 rotations per minute at a temperature of 37±0.5°C with a medium volume of 900 ml. The dissolution medium used was 40% v/v ethanol. The concentration of dissolved curcumin in each sample was analyzed using a UV-visible spectrophotometer.

3. Result and Discussion

Differences in the polymorphic form of pharmaceutical raw material can cause differences in the physicochemical properties, including solubility and dissolution rate (Zhou *et al.*, 2018). The powder X-ray diffractometer can be used to identify polymorphic forms of pharmaceutical raw materials (Egusa *et al.*, 2017). The crystalline solid form will show some peaks in the PXRD pattern, while the amorphous solid will not show any peaks. Based on the powder X-ray diffractogram, the curcumin raw material has a crystalline solid form with the major peaks at 2θ 8.9; 12.1; 17,2; 18.7, and 23.3 (**Figure 1**).

The location of these peaks corresponds to the form I of the curcumin polymorph (Tonnesen, Karlsen and Mostad, 1982). Like curcumin, the raw material of paracetamol used was also a crystalline solid with the major peaks at 2θ 12.1; 15.4; 18.0; 20.4; and 24.4 corresponding to the form I of paracetamol polymorph (Haisa *et al.*, 1976).

The mixing of curcumin and paracetamol was carried out by the wet grinding method in a stoichiometric ratio of 1:1 or equimolar using a small amount of solvent. This method is cheaper than methods involving many solvents, such as solvent evaporation and cooling crystallization and faster atomic reactions when compared to the dry grinding method (Patel, 2020). The condition for selecting the solvent used in this method is that the solvent must be able to dissolve at least the two components being mixed. Curcumin and paracetamol are soluble in ethanol (Priyadarsini, 2014; Romdhani *et al.*, 2020). Therefore, ethanol was used as a solvent in this wet grinding method.

The PXRD pattern of the curcumin-paracetamol (1:1) milling result in **Figure 2** did not show any new peaks that were different from the typical peaks of the two components and still showed a combination of peaks found in curcumin and paracetamol. This indicates that there is no interaction between curcumin and paracetamol which causes hydrogen bonds to form co-crystals. The co-crystal formation changes the PXRD pattern which is characterized by the appearance of new peaks and the disappearance of the peaks of the parent components (Alatas *et al.*, 2022).

Thermal analysis with DSC was carried out to demonstrate the existence of physical interaction between curcumin and paracetamol based on the thermogram of the two components. The DSC thermogram for curcumin, paracetamol, and the curcumin-paracetamol (1:1) milling result was shown in **Figure 3**. The DSC thermogram of curcumin exhibited an endothermic transition at 176.6°C which is the typical melting point of curcumin (Sayyar and Jafarizadeh, 2019). Like curcumin, the DSC thermogram of paracetamol also only showed one endothermic transition at 170.1°C which is the typical melting point of form I paracetamol (Sacchetti, 2001). The DSC thermogram of the curcumin-paracetamol (1:1) milling result showed a wide endothermic transition located below the melting point of curcumin and paracetamol. This wide endothermic transition at 151.2°C was not the melting point due to the co-crystal formation but was thought to be the melting point of the eutectic mixture of curcumin-paracetamol (1:1). Generally, co-crystals exhibit a sharp endothermic transition with the melting point between or below the melting points of the two materials being mixed.

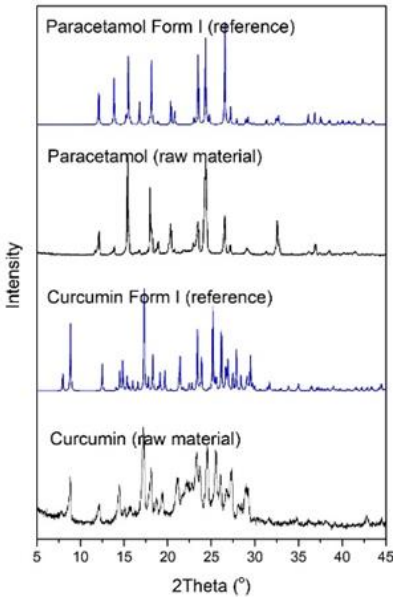

Figure 1. Powder X-ray diffraction pattern of curcumin and paracetamol raw materials compared with curcumin Form I (Tonnesen, Karlsen and Mostad, 1982) and paracetamol Form I (Haisa et al., 1976)

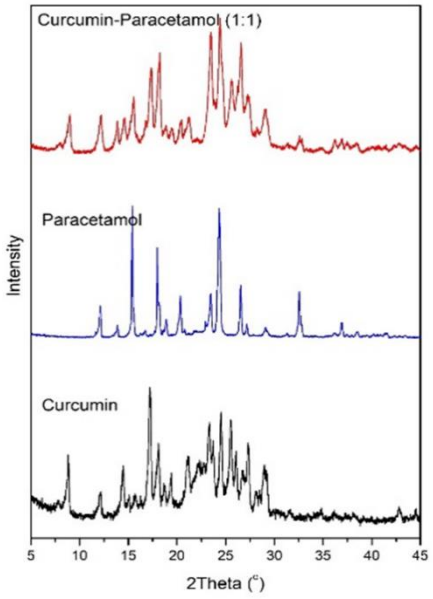

Figure 2. Powder X-ray diffraction pattern of curcumin, paracetamol, and curcumin-paracetamol (1:1) binary mixture

This situation also occurs in eutectic mixtures between curcumin and several other substances, including ferulic acid, hydroquinone, p-hydroxybenzoic acid, and tartaric acid at a 1:1 stoichiometric ratio (Goud *et al.*, 2012). One way to characterize the presence of physical interactions in the formation of co-crystal is to construct a phase solubility curve of one substance in a solution of another substance. The types of phase solubility curves introduced by Higuchi and Connors include A_L, A_P, A_N, B_S, and B_I (Higuchi and Connors, 1965). The phase solubility curves of type A (A_L, A_P, and A_N) demonstrate that the solubility of the substance will continue to increase and will not precipitate with increasing ligand concentration, while type B (B_I and B_S) show an increase in the solubility of the substance up to a certain concentration and precipitation begins to form co-crystal solid (Qiu *et al.*, 2017). The phase diagram of the solubility of curcumin in paracetamol solution in **Figure 4** corresponds to the A_L type.

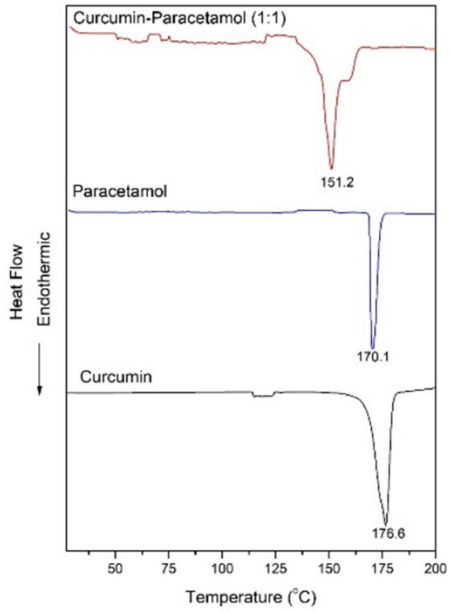

Figure 3. Differential scanning calorimetry thermogram of curcumin, paracetamol, and curcumin-paracetamol (1:1) binary mixture

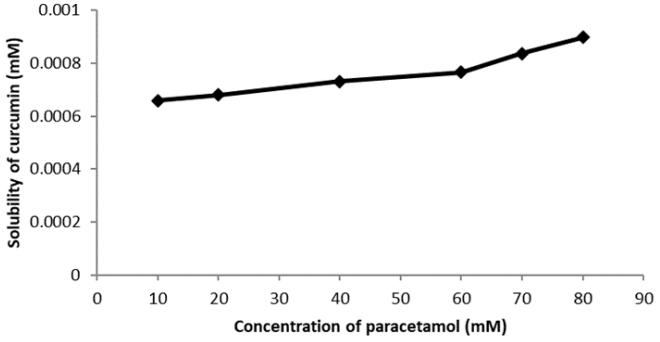

Figure 4. Phase solubility curve of curcumin in the various concentrations of paracetamol solutions in water

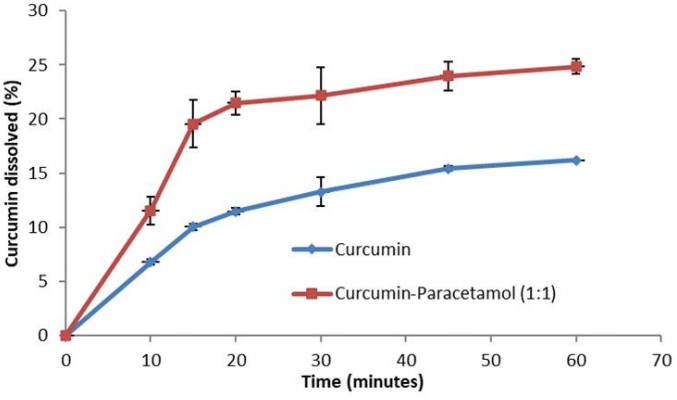

Figure 5. Dissolution profiles of curcumin that released from pure curcumin and curcumin-paracetamol (1:1) binary mixture (n=3)

The solubility of curcumin continued to increase with increasing paracetamol concentration. This showed that the physical interaction of the co-crystal solid formation between curcumin and paracetamol did not occur. The solubility test of the curcumin-paracetamol binary mixture (1:1) aims to determine the change in one of the important physicochemical properties as a result of mixing the two substances.

Table 1. Solubility of curcumin and curcumin-paracetamol (1:1) binary mixture in water at room temperature (n=3)

Materials	Solubility (µg/mL)
Curcumin	0.878 ± 0.083
Curcumin-Paracetamol (1:1)	7.266 ± 1.494

Table 1 showed the solubility of the curcumin-paracetamol binary mixture (1:1) was 8.3-folds higher than pure curcumin. This increase in solubility is caused by the formation of a simple eutectic mixture. The decrease in crystallinity and crystal size or it can also be caused by an increase in wettability (Hyun *et al.*, 2019; Bazzo, Pezzini and Stulzer, 2020).

Drug dissolution is strongly influenced by its solubility in the dissolution medium. The higher the solubility of the drug, the faster the dissolution rate. **Figure 5** showed the dissolution rate of the curcumin-paracetamol (1:1) binary mixture is faster than that of pure curcumin. Dissolved curcumin from curcumin-paracetamol (1:1) binary mixture for 60 minutes had reached 25%, while pure curcumin was only 16%. This is due to the higher solubility of curcumin-paracetamol (1:1) binary mixture than pure curcumin. The increase in the dissolution rate of curcumin previously also occurred due to the formation of a eutectic mixture with nicotinamide, hydroquinone, and ferulic acid (Goud *et al.*, 2012).

4. Conclusion

The characterization of wet grinding of the curcumin-paracetamol binary mixture at a stoichiometric ratio of 1:1 with the addition of a small amount of ethanol using a powder X-ray diffractometer and differential scanning calorimeter showed the formation of a simple eutectic mixture. The formation of this simple eutectic mixture has an impact on increasing the solubility and dissolution rate of curcumin.

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