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Original Article

PREPARATION OF SPRAY-DRIED MULTICOMPONENT CRYSTALS OF TRIMETHOPRIM-MANDELIC ACID AND ITS PHYSICOCHEMICAL CHARACTERIZATION

LILI FITRIANI[1], DENANDA SHINTANIA[2], HENDRIZAL USMAN[3], USWATUL HASANAH[4], ERIZAL ZAINI[5*]

[1,2,4,5]Department of Pharmaceutics. Faculty of Pharmacy. Universitas Andalas. Padang-25163, Indonesia. [3]Study Program in Pharmacy. Faculty of Pharmacy, Science and Technology. Universitas Dharma Andalas. Padang-25163, Indonesia
*Corresponding author: Erizal Zaini; *Email: erizal@phar.unand.ac.id

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ABSTRACT

Objective: Trimethoprim is a wide-spectrum antimicrobial compound belonging to Class II of the Biopharmaceutics Classification System (BCS), with high permeability but low solubility. This study aimed to prepare a multicomponent crystal (MCC) of trimethoprim-mandelic acid to enhance the solubility of trimethoprim.

Methods: MCC trimethoprim–mandelic acid was prepared by spray drying technique. Solid-state characterizations were performed by using Powder X-ray diffraction (PXRD), Differential Scanning Calorimetry (DSC), Fourier-transform infrared (FT IR) spectroscopy, Scanning Electron Microscopy (SEM), and polarized microscopy. The solubility test was performed in distilled water. The amount of dissolved trimethoprim was analyzed by High-Performance Liquid Chromatography (HPLC) using acetonitrile and phosphoric acid 1 % (10:90 v/v) as the mobile phase.

Results: MCC characterizations showed a different diffraction pattern from its intact materials according to PXRD analysis, a decrease in the melting point in the DSC thermogram, a shift of the wave number in the FT-IR spectra, and a new crystalline habit compared to the intact materials was presented by SEM analysis. The MCC also showed the color of interference under polarized microscopy, indicating the crystalline phase. The solubility of trimethoprim in MCC increased significantly by 3.98 times in comparison to intact trimethoprim.

Conclusion: The MCC trimethoprim-mandelic acid by spray drying technique enhanced the solubility of trimethoprim.

Keywords: Trimethoprim, Mandelic acid, Multicomponent crystal, Spray drying, Solubility

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INTRODUCTION

Trimethoprim is a wide-spectrum antimicrobial compound commonly used to treat pneumonia and urinary tract infections with a single use or combined with sulfonamides, which act as an inhibitor agent of dihydrofolate reductase (DHFR) that inhibits the conversion of dihydrofolic acid (DHF) into its active form, tetrahydrofolic acid (THF) [1]. Trimethoprim can be administered through various routes of administration. However, its low solubility in water limits the bioavailability of the drug when administered in oral dosage form [2]. Based on the Biopharmaceutical Classification System (BCS), trimethoprim is included in BCS class II, with low solubility and high permeability [3]. The solubility of trimethoprim is 0.04/100 ml in water [4].

Several methods have been conducted to modify the solubility of a pharmaceutical active ingredient (API), including reducing particle size, preparing in nanosuspension, using surfactant, forming salt, adjusting the pH, preparing into solid dispersion system, preparing into cocrystal or amorphous phase and forming the inclusion complexes [5]. Moreover, some investigations have been done to increase the solubility of trimethoprim, including the formation of inclusion complexes using β-cyclodextrin, which increase the solubility of trimethoprim 1.9 times [6, 7] and complexes with hydroxypropyl-cyclodextrin with solubility increase three times [8].

Amongst several methods that have been introduced, one method generally generates better physical and chemical properties compared to their intact active ingredients, known as the formation of multicomponent crystals [9]. Previous studies related to the formation of multicomponent crystals of trimethoprim have been investigated, including the formation of trimethoprim-sulfamethoxazole [10], trimethoprim-citric acid [11], and trimethoprim-maleic acid [12]. Our previous study also showed an improvement in trimethoprim solubility using mandelic acid as the co-former by solvent drop grinding method, which increased about 2.73 times [13].

One of the well-known and fast methods that has been developed in the formation of multicomponent crystals is spray drying. This method is usually used to produce dry powder from a solution or suspension through solvent drying in a fast time using hot air flow [14]. The growth or formation of crystalline multicomponent may occur due to a highly saturated state that is achieved in the very rapid evaporation of solvents process, the presence of a coformer, or the presence of interactions between the active substance and the coformer in the liquid phase [14]. One of the advantages of this method is that the resulting multicomponent crystals can be adjusted by optimizing several parameters contained in the spray dryer, such as inlet temperature, outlet temperature, flow rate, and concentration of the feed solution [15].

The characteristics of multicomponent crystals are influenced by several factors, including the structure and properties of the coformer used [16, 17]. This study used mandelic acid as a coformer to form multicomponent crystals. Mandelic acid belongs to the monocarboxylic acid group, precisely α-hydrocarboxylic acid (AHA), which has a hydroxyl group so that it has the ability to form hydrogen bonds, which are one of the main factors in the formation of multicomponent crystals [18]. Moreover, the possibility of hydrogen bond formation can predict the formation of multicomponent crystals of trimethoprim and mandelic acid. The formation of MCC can also be expected through a ΔpKa-based model approach. At ΔpKa value>3, salt formation tends to occur. Meanwhile, there is a possibility of cocrystal formation in the range of 0<ΔpKa<3 [17]. Mandelic acid has several activities, including antimicrobial, anti-tumor, and anti-inflammatory [18, 19]. The multi-component crystal formation of trimethoprim-mandelic acid has the potential to provide a synergistic effect as an antimicrobial and can increase the solubility of trimethoprim. Thus, in this study, we prepared the MCC of trimethoprim with mandelic acid by spray drying technique with aimed to increase the solubility of trimethoprim and characterize the MCC by solid-state characterization, including thermal analysis by Differential Scanning Calorimetry (DSC), crystallinity analysis by Powder X-ray Diffraction, morphology analysis by Scanning Electron Microscope (SEM) and polarized microscope, and functional groups by infra-red

(IR) spectrophotometry.

MATERIALS AND METHODS

Materials

Trimethoprim was obtained from PT Kimia Farma (Indonesia). Mandelic acid was purchased from Sigma-Aldrich (USA). Ethanol and acetonitrile pro analysis were purchased from Merck (Germany).

Methods

Formation of MCC trimethoprim-mandelic acid

Trimethoprim and mandelic acid were weighed in a ratio of mol 1:1. Trimethoprim was then dispersed into ethanol solvent, while mandelic acid was dispersed into distilled water. The result of the dispersion obtained was then mixed and homogenized by stirring. The mixture was then dried using a spray dryer apparatus (Buchi mini spray dryer B-290, Switzerland). The apparatus was set at an inlet temperature condition of 90 °C with a flow speed of 35 m^3/h. The nozzle size of the spray drying tool used was 0.7 mm. The drying result was stored in a container and then in a desiccator.

The physical mixture of trimethoprim and mandelic acid was also prepared at the same amount and ratio by mixing the mixture in a jar and kept in a desiccator for further characterization, similar to MCC by spray drying.

Physicochemical characterization of MCC trimethoprim-mandelic acid

X-ray diffraction analysis

Powder x-ray diffraction analysis of intact trimethoprim, mandelic acid, a physical mixture, and MCC of trimethoprim-mandelic acid were carried out at room temperature with the following conditions set: metal target Cu, filter Kα, voltage 45 kV, current 40 mA. Measurements were carried out in the range of 2θ 5-50^0 (PAN analytical MPD PW3040/60 type X"Pert Pro, Netherland).

Differential scanning calorimetry (DSC) analysis

Thermal analysis for characterization of intact trimethoprim, mandelic acid, a physical mixture, and MCC of trimethoprim-mandelic acid were carried out using the DSC apparatus (Shimadzu DSC-60 Plus, Japan). The DSC device was set at a temperature range of 30-240 °C with a heating speed of 10 °C per minute.

Fourier-transform infrared (FTIR) spectroscopic analysis

Small amounts of intact trimethoprim, mandelic acid, a physical mixture, and MCC of trimethoprim-mandelic acid were analyzed by infrared spectrophotometer (Shimadzu IR Tracer 100, Japan). The analysis was conducted by dispersing the sample on a KBr plate pressed with high pressure (hydraulic suppressor). The absorption spectrum was then recorded at a wave number of 4000-400 cm^{-1}.

Scanning electron microscope (SEM) analysis

The SEM analysis was carried out for intact trimethoprim, mandelic acid, a physical mixture, and MCC trimethoprim-mandelic acid. The powder sample was placed on the aluminum sample holder and coated with gold or palladium. Samples were then observed at various magnifications on the SEM apparatus (Hitachi FLEXSEM 100, Japan). The voltage is set at 20 kV with a current of 12 mA.

Analysis with polarized microscopy

Analysis with polarized microscopy was carried out for trimethoprim, mandelic acid, a physical mixture, and MCC trimethoprim-mandelic acid by preparing a sample on the glass of the object, and then the sample was observed under a microscope (Axioscope, USA) with a magnification of 20x.

Solubility test

Excess amounts of intact trimethoprim, physical mixture, and MCC of trimethoprim-mandelic acid were each added to 100 ml of distilled water. The sample was shaken using a sonicator for 5 min and further filtered with 0.45 µm Whatman filter paper. The result was then analyzed using HPLC (Shimadzu AUX 220, Japan) using acetonitrile and phosphoric acid 1 % (10:90 v/v) as the mobile phase and the amount of trimethoprim dissolved was detected at a wavelength of 287 nm. The test was conducted in triplicate.

RESULTS AND DISCUSSION

Powder X-ray diffraction analysis

X-ray diffraction analysis was performed to identify the crystalline phases, as this technique is prominent in solid-state characterization [20]. Generally, each crystalline compound will depict different diffractogram patterns as their particular characteristic [21]. The diffractogram pattern of each sample as seen in fig. 1.

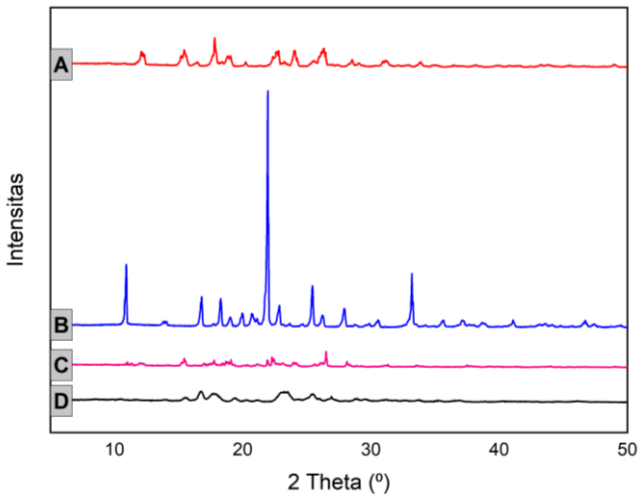

Fig. 1: PXRD diffractogram of a) Trimethoprim, b) Mandelic acid, c) Physical mixture, d) Multicomponent crystals

Trimethoprim shows specific peaks at a diffraction angle of 15.458^0; 17.811^0; 19.085^0; 22.803^0; 24.012^0; 26.287^0 and 26.496^0, whereas mandelic acid has definite peaks at 10.921^0; 16.797^0; 21.958^0; 25.442^0. The physical mixture shows the same pattern as the intact materials, while multicomponent crystals show several new peaks at a diffraction angle of 16.475^0; 17.811^0; 19.423^0, 23.912^0, 25.481^0, and 26.911^0. The existence of different peaks than the intact materials also occurred in previous studies regarding the MCC formation of trimethoprim with malic acid and citric acid [11, 22]. The diffractogram patterns with new peaks in this study indicated

the changes in the crystal lattice that occur due to the solid-state interaction between trimethoprim and mandelic acid molecules [13]. The type of multicomponent crystal formed in this research was likely the salt-type crystal according to the pKa rules [13, 23].

Differential scanning calorimetry (DSC) analysis

Differential Scanning Calorimetry (DSC) analysis is one considerable method in analyzing the thermal properties of samples, as this method shows endothermic or exothermic peaks typical of the sample being investigated [24]. The trimethoprim and mandelic acid thermogram in fig. 2 shows a single endothermic peak at 202.86 °C and 121.74 °C, respectively, which is the value of the melting point. The physical mixture's thermogram had two endothermic peaks at 167.89 and 170.48 °C. These peaks show that the two components in the physical mixture melted at different temperatures due to the absence of interactions between the two compounds. The MCC of trimethoprim-mandelic acid shows a sharp endothermic peak between the melting point of its intact materials at 171.56 °C. A pharmaceutical active ingredient's melting point is related to the crystalline phase's lattice energy [25]. The decrease in the melting point resulting from intramolecular interactions between trimethoprim and mandelic acid, which leads to changes in the structure and crystallinity of the multicomponent crystals compared to intact trimethoprim [11, 13].

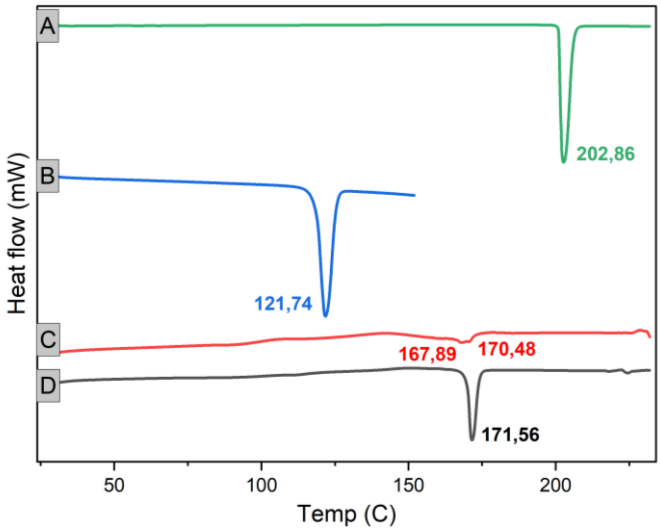

Fig. 2: DSC thermogram of a) Trimethoprim, b) Mandelic acid, c) Physical mixture, d) Multicomponent crystals

Fourier-transform infrared (FT-IR) spectroscopic analysis

One of the most important techniques for identifying and examining the configuration or conformation of functional groups in a sample is infrared spectroscopy [26]. Trimethoprim showed a several peak transmittance at wave numbers 3468.01 cm^{-1} (NH), 3103.46 cm^{-1} (OH), 1633.71 cm^{-1} (C=C aromatic), 1456.26 cm^{-1} (CH_2), 1263.37 cm^{-1} (C=N), 1234.4 cm^{-1} (OCH_3), 1456.26 cm^{-1} (CH_2), while mandelic acid at wave numbers 3072.60 cm^{-1} (R-OH), 2875.86 cm^{-1} (COOH), 1705.07 cm^{-1} (C=O), and 1452.40 cm^{-1} (CH_2) as seen in fig. 3. The physical mixture shows a similar peak as trimethoprim and mandelic acid, and there was no significant shift in the wave number. Meanwhile, the MCC of trimethoprim-mandelic acid showed a shift in the wave number that occurred in the NH group from 3468.01 to 3350 cm^{-1}. A similar case also happened in the formation of MCC of trimethoprim-malic acid, which indicated a stretch in the NH group [22].

A shift also occurred in the wave number 3103.46 cm^{-1} to 3138.18 cm^{-1} with a wider band indicating an OH stretch. Based on the previous study, these intermolecular interactions can occur between OH in carboxylic acids and N atoms [27, 28].

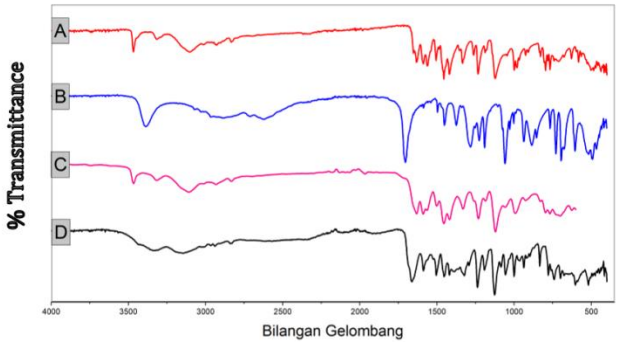

Fig. 3. FTIR spectrum of a) Trimethoprim b) Mandelic acid c) Physical mixture d) Multicomponent crystals

A carboxylic anion band at wave number 1587.42 cm^{-1} and a wide band in the wave number range 2700-2200 cm^{-1} was formed due to the presence of protonated carboxylic and nitrogen anions. Studies of trimethoprim modifications show the same result that may indicate the presence of hydrogen bonds (OH–N) between the protonated pyrimidine of the trimethoprim cation and the carboxylic anion of mandelic acid [22]. It can be concluded that the result that formed in this study is a salt-type multicomponent

crystal. The existence of this interaction is supported by analytical data with DSC showing a decrease in melting point and analysis with PXRD, which shows a different diffraction pattern for the MCC of trimethoprim-mandelic acid.

Scanning electron microscope (SEM) analysis

SEM is one of the qualitative methods used to observe the structure or morphology of materials [8]. The results of the morphological analysis of the trimethoprim, mandelic acid, physical mixture, and MCC are shown in fig. 4. The results of the SEM analysis show that the habit of trimethoprim crystals was irregular block or cubic. A similar form was also observed in several studies about the formation of MCC [11, 22]. Mandelic acid shows a form of block with rounded corners and a smooth surface. The combination of trimethoprim and mandelic acid crystal can be observed in the results of the analysis for the physical mixture. MCC trimethoprim-mandelic acid shows a new crystal habit that differs from its intact components with a rougher surface.

Change in the habits of the multicomponent crystals is likely due to the interaction between trimethoprim and mandelic acid. The particle size of the resulting multicomponent crystals is also smaller than its starting materials, and this can be observed based on the scale indicated in the SEM results of MCC trimethoprim-mandelic acid. The spray drying process influences this particle size reduction; when a solution of the trimethoprim-mandelic acid mixture passes through the nozzle, the resulting particles will likely be the same or smaller than the nozzle size.

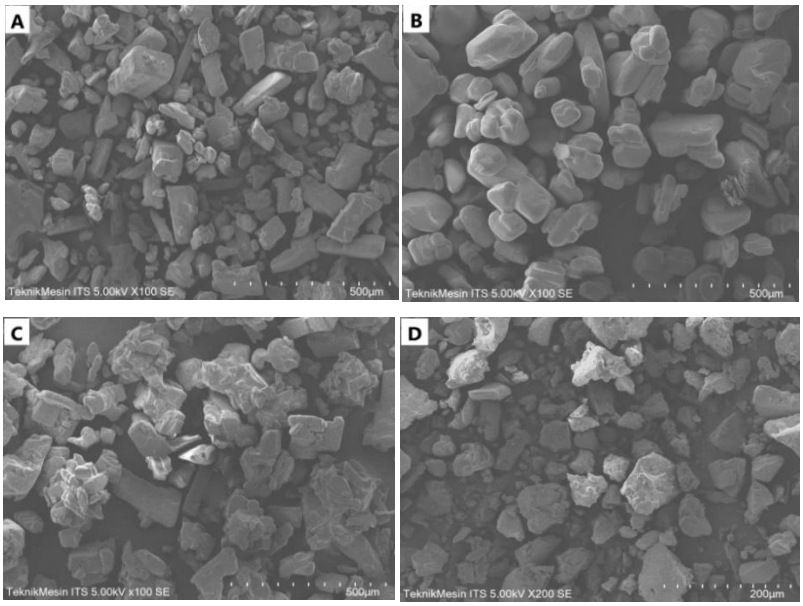

Fig. 4: SEM analysis of a) Trimethoprimic, b) Mandelic acid, c) Physical mixture, d) Multicomponent crystals

Analysis with polarizing microscope

Polarized microscopy can be used to determine whether a compound is crystalline or amorphous. Crystalline samples will show a double refraction when observed under a polarizing microscope, giving results with various colors due to refracted light. The emitted color is referred to as the interference color [29].

Fig. 5 shows the results of microscopic observations of trimethoprim, mandelic acid, a physical mixture, and MCC of trimethoprim-mandelic acid. The particles of each sample emitted various interference colors. It can be concluded that the samples are all in the crystalline phase. Fig. 5D also shows particles with a smaller size due to the friction between each compound in the mixing and spray-drying process.

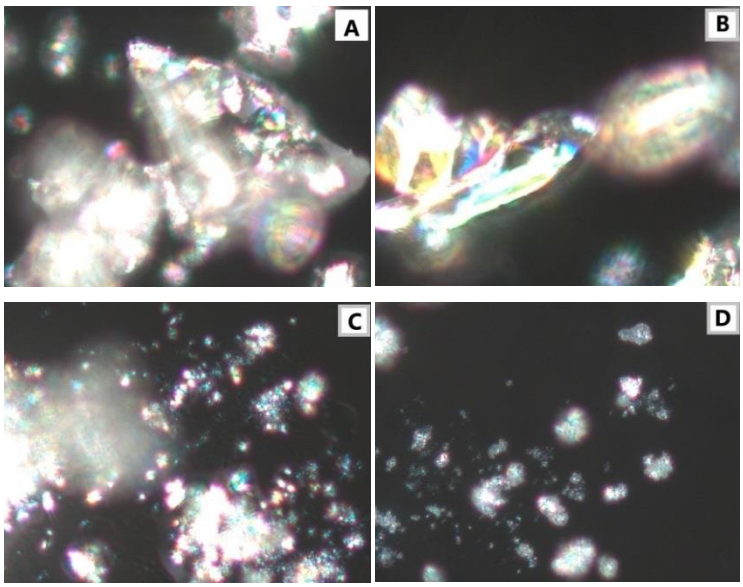

Fig. 5: Micrograph on a polarizing microscope of a) Trimethoprimic, b) Mandelic acid, c) Physical mixture, d) MCC

Table 1: The results of the solubility test

Samples	Solubility of trimethoprim±SD	Increase in solubility (times)
Trimethoprim	62.252±0.017 (mg/100 ml)	-
Physical Mixture	112.937±0.063 (mg/100 ml)	1.81
Multicomponent crystals	247.747±0.006 (mg/100 ml)	3.98

Solubility test

The solubility test results showed that trimethoprim in the form of a physical mixture and multicomponent crystals are respectively 1.81 and 3.98 times more soluble than intact trimethoprim, as seen in table 1. The improvement in solubility of trimethoprim in MCC can be influenced by several factors, including the co-former used, a decrease in crystallinity, a change in the crystal lattice, and a reduction in particle size. Mandelic acid used as a coformer in the multicomponent formation of these crystals is water-soluble [30]. Based on previous studies, using water-soluble coformers causes crystals to be more hydrophilic. Thus increasing its affinity in the water solvent and causing its solubility to increase [11]. The decrease in melting point and powder X-ray diffraction intensity obtained in this study indicate a weaker reduction in the crystal lattice energy. The weaker lattice energy causes the crystal to dissolve more efficiently, increasing solubility [11]. The methods and solvents used to form multicomponent crystals also influence the size of the particles produced. Theoretically, the small nozzle size of the apparatus will produce small droplets as well, thus causing the resulting particles to be smaller than intact trimethoprim. It is also one of the causes of increased trimethoprim solubility in the multicomponent crystals. Particles of smaller size have a larger surface area, thereby increasing the contact between the particles and the solvent [31]. These significant results are expected to have a greater impact on pharmacological activities such as dose adjustments.

CONCLUSION

Based on the results of characterization with DSC, PXRD, FT-IR spectroscopy, SEM analysis, and polarized microscopy in this research, it can be concluded that salt-type multicomponent crystals of trimethoprim-mandelic acid were formed. MCC of trimethoprim-mandelic acid also showed an improvement in solubility compared to intact trimethoprim.

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Nil

AUTHORS CONTRIBUTIONS

Conceptualization, E. Z., UH, L. F.; methodology, E. Z., L. F., D. S., U. H., and H. U., formal analysis, L. F., E. Z., D. S, and U. H.; resources, E. Z. and L. F.; writing-original draft preparation, L. F., E. Z. and D. S.; writing— review and editing, L. F., E. Z., supervision, E. Z; funding acquisition, E. Z. and L. F. All authors have read and agreed to the published version of the manuscript.

CONFLICT OF INTERESTS

The authors declare no conflict of interest.

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