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Original Article

FORMATION AND CHARACTERIZATION OF MULTICOMPONENT CRYSTAL OF TRIMETHOPRIM AND MANDELIC ACID BY SOLVENT DROP GRINDING METHOD

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ABSTRACT

Objective: To increase the solubility of trimethoprim by forming multicomponent crystals using mandelic acid as a coformer.

Methods: Multicomponent crystals of trimethoprim and mandelic acid were prepared at a ratio of 1:1 mol by the Solvent Drop Grinding (SDG) method. Solid state characterization was carried out using Differential Scanning Calorimetry (DSC), Powder X-ray Diffraction (PXRD), Fourier Transform Infrared (FTIR) spectroscopy, Scanning Electron Microscope (SEM), and polarized microscope. The solubility test of trimethoprim was carried out in CO_2-free distilled water using a sonicator for 5 min and then determined by High-Performance Liquid Chromatography (HPLC) using acetonitrile and phosphoric acid in a 10:90 ratio as the mobile phase and octadecylsilane (C18) as the stationary phase.

Results: The results showed a decrease in the melting point and enthalpy of fusion on the DSC thermogram, a new peak in the X-ray diffraction pattern, and a slight shift of wave number in the FTIR spectroscopy. Those characterizations indicated that the multicomponent crystal formed a salt type. SEM analysis showed morphological changes and formation of new crystal habits. The polarization microscopy analysis showed birefringent with various colors in all samples. The solubility of multicomponent crystal is 2.73-times higher compared to intact trimethoprim.

Conclusion: The formation of cocrystals of trimethoprim and mandelic acid by SDG method increased the solubility of trimethoprim.

Keywords: Trimethoprim, Mandelic acid, Multicomponent crystal, Solvent drop grinding, Solubility

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INTRODUCTION

Trimethoprim, also known as 5-[(3,4,5-trimethoxyphenyl) methyl] pyrimidine-2,4-diamine, is a broad-spectrum antimicrobial compound that is a synthetic agent that acts as an inhibitor of the bacterial dihydrofolate reductase enzyme, which still used clinically alone or in combination with sulfonamides [1, 2]. Trimethoprim is still used due to its relatively low cost and ability to combat common bacterial diseases effectively, even though newer antibacterial and antimicrobial medications have replaced this combination [3].

One important factor in achieving the drug concentration in systemic circulation to produce a pharmacological effect is solubility [4]. Trimethoprim has very low solubility in water, 0.04; methanol 1.21; acetone 0.35; and 0.81 g/100 ml ethanol at 25 °C [5]. A compound with low solubility in water causes poor absorption in the gastrointestinal tract and low bioavailability. Therefore, some investigations have been carried out to increase the solubility of poorly water-soluble drugs, which is a challenge in developing into pharmaceutical dosage forms. Solid dispersion, complexation, lipid-based systems, micronization, nanonization, and multicomponent crystals are just a few of the methods that have been developed to improve the solubility of drugs that are difficult to dissolve in water [6].

Various studies to increase the solubility of trimethoprim that have been conducted include the formation of inclusion complexes with cyclodextrin [1, 2] and hydroxypropyl-cyclodextrin [7] and the formation of cocrystals of trimethoprim with nicotinamide [8]. The formation of inclusion complexes of trimethoprim with 16 mmol-cyclodextrin increased the solubility by 1.9 times [1], and the formation of inclusion complexes with 28.6 mmol hydroxypropyl-cyclodextrin increased the solubility of trimethoprim up to 3 times [7]. The dissolution rate of trimethoprim was about 1.3 times higher when it was co-crystallized with nicotinamide coformers [8].

One method that is currently being developed to enhance a compound's physicochemical properties is the formation of multicomponent crystals. By altering the crystal structure without affecting the drug's pharmacological activity, multicomponent crystals can improve physical and chemical stability while improving solubility, dissolution rate, compressibility, and other physicochemical properties [9]. Multicomponent crystals consist of solvates, hydrates, salts, and cocrystals. The selection of suitable coformers that are able to interact with drug compounds to form new crystals is the process by which multicomponent crystals are formed [10]. A cocrystal is a crystalline complex consisting of two or more neutral molecular constituents bonded together in a crystal lattice by noncovalent interactions (often used as hydrogen bonding) [11]. Salt is a multi-component system in which a proton is transferred from an acid to a base in an ionic state [12]. The transfer of protons between drug compounds and coformers is the difference between cocrystals and salts [13]. Increasing drug solubility with the formation of multicomponent crystals has been widely carried out and has proven successful. One of them was the study of the formation of multicomponent crystals of trimethoprim and malic acid, which showed that trimethoprim was 2.5 times more soluble [14].

Mandelic acid is a hydrophilic compound. The solubility of mandelic acid is 158.7 mg/ml in water, 1000 mg/ml in ethanol, and very soluble in ether or isopropyl alcohol [15]. The use of mandelic acid as a coformer has previously been carried out with nicotinamide [16], levetiracetam [17, 18], meloxicam [19], and isoniazid [20]. Analysis of the coformer structure of mandelic acid showed that the hydroxyl (carboxylic) group in mandelic acid was predicted to form hydrogen bonds with pyrimidine groups in trimethoprim [21]. The choice of mandelic acid as a coformer was also expected through a pKa-based model approach, where trimethoprim had a pKa value of 7.12 and mandelic acid had a pKa value of 3.75 [22, 23]. In general, if $\Delta pKa>3$, salt is probably formed. On the other hand, in the range $0<\Delta pKa<3$, cocrystals or possible salts may form [24]. In addition, mandelic acid is also known to have antimicrobial activity [21]; this activity is expected to work synergistically with the antimicrobial effectiveness of trimethoprim.

Multicomponent crystals of trimethoprim and mandelic acid will be prepared using the solvent drop grinding method. The solvent drop grinding method is more efficient due to several factors, including shorter time in preparation, cost-effectiveness (the number of samples required is small), and environmental friendly [25, 26]. In this study, multicomponent crystals of trimethoprim and mandelic acid are expected to increase trimethoprim's solubility. The

multicomponent crystals formed were characterized by thermal analysis using Differential Scanning Calorimeter (DSC), X-ray diffraction pattern analysis, IR spectroscopy analysis, morphological analysis by Scanning Electron Microscopy (SEM), microscopic analysis by polarization microscopy, and solubility test.

MATERIALS AND METHODS

Materials

Trimethoprim (PT Kimia Farma, Indonesia), mandelic acid (Sigma-Aldrich, USA), methanol (Merck, Germany), acetonitrile pro analysis (Merck, Germany), water for injection (PT Ikapharmindo Putramas, Indonesia), phosphoric acid (Merck, Germany), and distilled water.

Preparation of multicomponent crystals of trimethoprim and mandelic acid

Trimethoprim and mandelic acid were weighed 1:1 mol (0.290g: 0.152g) to prepare multicomponent crystals. The binary mixture were ground manually for 10 min while adding 10 drops methanol. For further characterization, the multicomponent crystals were stored in a tightly sealed container and kept in a desiccator.

Characterization of solid-state properties

Differential scanning calorimetry analysis

Thermal analysis of the samples was carried out using a Differential Scanning Calorimeter (Shimadzu DSC-60 Plus, Japan), which has been calibrated with Indium. On a closed aluminum plate, a 4 mg sample was placed. The temperature of DSC was set in a range of 30-250 °C at a heating rate of 10 °C per minute. Analysis was carried out on samples of trimethoprim, mandelic acid, and multicomponent crystals of trimethoprim and mandelic acid.

X-ray diffraction analysis

X-ray diffraction analysis of the sample powder was carried out at room temperature using a Powder X-Ray Diffraction (PANanalytical MPD PW3040/60 type X' Pert Pro, the Netherlands), with the following measurement conditions: Cu metal target, Kα filter, voltage 40 kV, current 40 mA, analysis was carried out in the range 2θ of 0-50^0. The sample was placed in a sample holder and leveled to prevent particle orientation during sample preparation. Samples of trimethoprim, mandelic acid, and multicomponent crystals of trimethoprim and mandelic acid were subjected to analysis.

Fourier transform infrared (FT IR) analysis

Infrared spectroscopy (Shimadzu IRTracer-100, Japan) was used to analyzed trimethoprim, mandelic acid, and multicomponent crystals of trimethoprim and mandelic acid. The sample was spread out on a KBr plate that was compressed with high pressure (hydraulic press). Wave numbers between 4000-600 cm^{-1} were used to capture the absorption spectra.

Scanning electron microscopy analysis

The crystal habits were investigated by SEM (Hitachi FLEXSEM 100, Japan). The powder sample was placed in an aluminum sample holder coated with gold. The samples were then observed at various instrument magnifications, with a voltage of 20 kV and a current of 12 MA. Samples of trimethoprim, mandelic acid, and multicomponent crystals of trimethoprim and mandelic acid were analyzed.

Polarizing microscope analysis

The analysis was carried out using a polarizing microscope (Olympuss, Japan) by preparing the sample on a glass slide. Trimethoprim, mandelic acid, and multicomponent crystals of trimethoprim and mandelic acid then was observed under cross-polarized light on a polarizing microscope with a magnification of 20x.

Solubility test

Excessive amount of trimethoprim and multicomponent crystals of trimethoprim and mandelic acid were weighed in order to obtain saturated condition. The solubility test of was determined in 100 ml CO2-free distilled water for five minutes then filtered using 0.45 µm Whatman filter paper. The sample was injected into the HPLC instrument (Shimadzu AUX 220, Japan) using UV detector. The stationary phase was octadecylsilane (C18) and the mobile phase was acetonitrile and phosphoric acid in a ratio of 10:90 and trimethoprim was detected at a wavelength of 287 nm. The solubility test was carried out triplicated and the significancy was test statistically using one-way ANOVA.

RESULTS AND DISCUSSION

Differential scanning calorimetry analysis

The thermodynamic changes occur when a substance heated or cooled is used to analyze thermal properties. The change in the melting point of the binary mixture of the active pharmaceutical ingredients and coformer likely indicates the presence of solid-state interactions [27]. The presence of a new crystalline phase can also be predicted through DSC analysis, in which the melting point is between the melting points of the pure compound [28]. Thermogram data of trimethoprim, mandelic acid, and multicomponent crystals of trimethoprim and mandelic acid is seen in fig. 1.

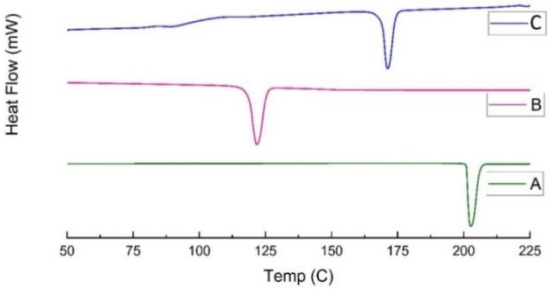

Fig. 1: DSC Thermogram of A). Trimethoprim, B). Mandelic acid, and C). Multicomponent crystals of trimethoprim and mandelic acid

The presence of a single sharp endothermic peak at 171.21 °C, which was between the melting points of trimethoprim (202.66 °C) and mandelic acid (121.74 °C), supported the prediction that a new crystal phase emerge in the multicomponent crystals of trimethoprim and mandelic acid. In addition, the value of the enthalpy of fusion of the sample can also be known by DSC analysis. The multicomponent crystals had a decrease in the enthalpy fusion from intact trimethoprim (105.37 J/g) and mandelic acid (148.93 J/g) to 45.8 J/g, which indicated the less amount of energy required to melt the multicomponent crystals [29]. The reduction in the degree of crystallinity can also be caused by the influence of grinding process in formation of multicomponent crystals [30].

X-ray diffraction pattern analysis

X-ray diffraction pattern analysis is a technique for characterizing the solid-state properties of a compound, such as the crystalline phase, amorphization, and interactions between solids [31]. Each crystalline compound has unique characteristics in its diffractogram pattern [32]. Through the analysis of X-ray diffraction patterns, data on decreasing the degree of crystallinity and confirmation type of multicomponent crystals formation can also be investigated. The formation of new crystalline phases like cocrystals or salts is indicated by alterations in the X-ray diffraction pattern in solids caused by intermolecular interactions within lattice crystal [28]. The diffraction pattern analysis of trimethoprim, mandelic acid, and multicomponent crystals of trimethoprim and mandelic acid can be seen in fig. 2.

Trimethoprim had sharp, specific peaks at 12.13°, 15.45°, 17.82°, 18.80°, 22.76°, 24.04°, and 26.34°, while mandelic acid had a specific peak that is sharp at 10.92°, 16.80°, 18.28°, 21.96°, and 25.44°. There were new peaks in the multicomponent crystals of trimethoprim and mandelic acid, which were positioned differently from the peaks of intact trimethoprim and mandelic acid, at positions 2θ of 10.72°, 13.45°, 16.52°, 17.26°, 24.61°, 25.19°, 25.58°, and 26.65°. These

peaks indicated the formation of a new crystalline phase in the multi-component sample. According to the ΔpKa rules, the difference in pKa between trimethoprim and mandelic acid is 3.37 which likely form a salt-type multicomponent crystal [24]. Moreover, to form salt-type, the conjugate acid must have a pKa value that is lower than the conjugate in order for sufficient proton transfer from the acidic to the base [12].

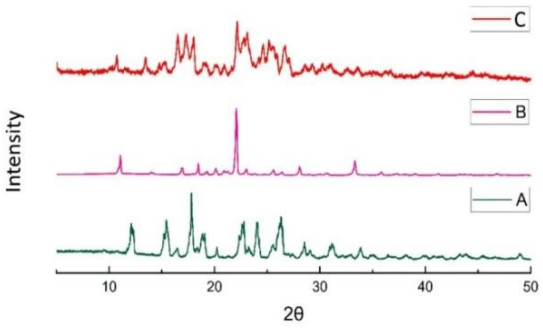

Fig. 2: Diffractogram of A). Trimethoprim, B). Mandelic acid, and C). Multicomponent crystals of trimethoprim and mandelic acid

Fourier transform infrared (FTIR) analysis

IR spectroscopy is one of the most critical analyses in determining the crystal structure's conformation [32]. Due to the formation of hydrogen bonds, interactions between components in a crystalline multicomponent system are characterized in infrared spectroscopy by a shift in the wavenumber [33]. The physical interaction of trimethoprim and mandelic acid can be seen in fig. 3.

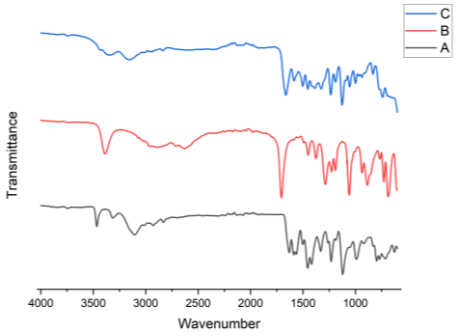

Fig. 3: FT-IR spectrum of A). Trimethoprim, B). Mandelic acid, and C). Multicomponent crystals of trimethoprim and mandelic aci

Table 1: Comparison of the wave numbers of trimethoprim, mandelic acid, and multicomponent crystals of trimethoprim and mandelic acid

Functional groups	Wavenumber range (cm^{-1})	wave numbers (cm^{-1})		
		Trimethoprim	Mandelic acid	Multicomponent crystals
N-H, OH	3750-3000	3467,3314, 3106 (N-H)	3388 (O-H)	3345 (N-H), 3155(O-H)
C=O	1900-1650	-	1706	1664
C=C, C=N stretching	1675-1500	1630, 1589, 1502	-	2838
C-H bending	1475-1300	1456, 1418, 1332	1451, 1376	1502, 1455, 1391
C=C bending	1000-650	991, 915	937, 886	1000, 938, 833

The difference between intact trimethoprim and mandelic acid can be seen in the wave number range from 3500 to 3000 cm^{-1}. In the spectrum of multicomponent crystals of trimethoprim and mandelic acid, there was a shift in the wave number of the N-H group from pure trimethoprim 3467 cm^{-1} to 3345 cm^{-1}, a shift in the O-H wave number from 3388 cm^{-1} to 3155 cm^{-1}, this indicated the possibility of hydrogen bonding. The formation of multicomponent crystals of trimethoprim with malic acid conducted by Yuliandra *et al.*, hydrogen bond formation occurs through N–H … O between the protonated pyrimidine cation in trimethoprim and the carboxylic anion of malic acid [14]. Similar interactions are also predicted in the formation of multicomponent crystals of trimethoprim and mandelic acid in this study.

Scanning electron microscopy (SEM) analysis

Characterization using SEM was carried out to observe the surface morphology of the sample [20]. Fig. 4 presents the results of the SEM analysis of intact trimethoprim and mandelic acid at 100x magnification and multicomponent crystals of trimethoprim and mandelic acid at 200x magnification. It can be seen that the morphology of trimethoprim is a bean shape with irregular surface sides and non-uniform size. Meanwhile, mandelic acid has a rough shape with an uneven surface. The multicomponent crystals of trimethoprim and mandelic acid have a slightly different shape from the intact substances, in which the particles are almost spherical, with a rough surface and have a smaller but not uniform size.

The phenomenon of the grinding process can alter the shape and size of multicomponent crystals compared to its intact due to the mechanical energy used during the grinding that may change not only the morphology of the multicomponent crystals but also others properties, including thermal and x-ray diffraction as previously described [34].

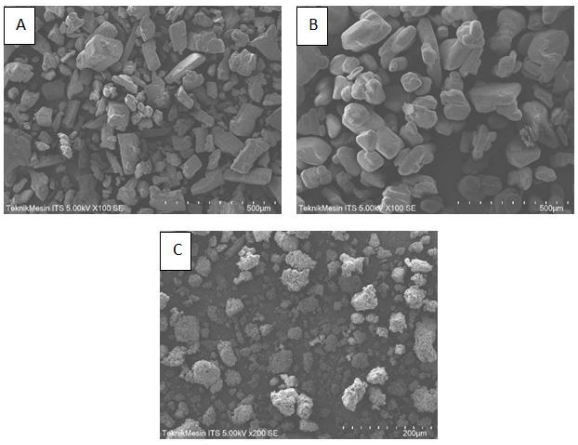

Fig. 4: SEM morphology of A). Trimethoprim, B). Mandelic acid, and C). Multicomponent crystals of trimethoprim and mandelic acid

Polarizing microscope analysis

Analysis using a polarizing microscope is intended to ensure the crystalline phase of the sample. The double refractive index (birefringent) is only occur on crystalline solid [35], in which it will give color during observation on a polarizing microscope. In contrast, the amorphous phase will not show color due to the irregular arrangement of the crystal lattice [36]. The polarization microscopy analysis of trimethoprim, mandelic acid, and multicomponent crystals of trimethoprim and mandelic acid at a 20x magnification is depicted in fig. 5. All samples showed variegated colors, which proved that the solid was still in the crystalline phase.

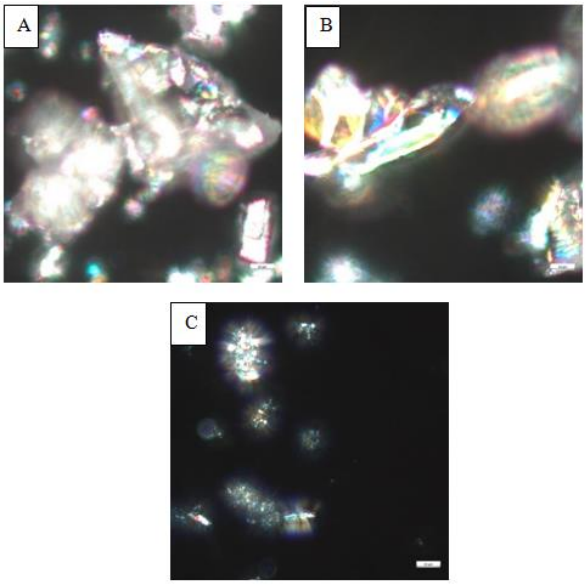

Fig. 5: Microscopic form A. Trimethoprim, B. Mandelic acid, C. Multicomponent crystals of trimethoprim and mandelic acid

In addition, the observations using a polarizing microscope can also show the difference in crystal habit between intact compounds and multicomponent crystals. Compared to intact compounds, the multicomponent crystals in fig. 5 have distinct shapes and colors, indicating that a new crystalline phase was formed as a result of the interaction between trimethoprim and mandelic acid. This has also been proven in DSC, XRD, and FTIR analyses in the previous explanation.

Solubility test

The solubility test was intended to determine the enhancement on trimethoprim's solubility in multicomponent crystal, which used mandelic acid as coformer and solvent drop grinding as the preparation method. The solubility result can be seen in table 2. Trimethoprim's solubility in CO_2-free distilled water increased by 2.73 times higher in the multicomponent crystals of trimethoprim and mandelic acid compared to intact trimethoprim.

One mechanism that affects the increase in solubility is change in thermodynamic properties (melting point and enthalpy fusion). The melting point is related to the lattice energy of the crystal, a decrease in the melting point indicates the weakening of the lattice energy in the crystalline phase of the compound so that there is an increase in solubility [31]. In this study, decreasing the melting point of multicomponent crystals of trimethoprim and mandelic acid proved the effect on increasing the solubility. In addition, the increase in solubility is also influenced by choice of a coformer. In this study, mandelic acid has high solubility in water that is estimated affect the increase in the solubility trimethoprim multicomponent crystals. The multicomponent crystals tend to be more hydrophilic and have better affinity in water, thus salt-based compounds will split into cationic and anionic ions [27].

Table 2: The results of the solubility test

Samples	Solubility of trimethoprim±SD (mg/100 ml)	Enhancement solubility
Trimethoprim	94.57±0.500	-
Multicomponent crystals of trimethoprim and mandelic acid	258.23±0.102	2.73 times

n = 3

CONCLUSION

This study shows that the formation of multicomponent crystals of trimethoprim and mandelic acid in a ratio mol of 1:1 using the solvent drop grinding method resulted in a salt-type multicomponent crystal, based on the results of thermal, X-ray diffraction, IR spectroscopic, morphological analysis. Multicomponent crystals of trimethoprim and mandelic acid by solvent drop grinding increase the solubility by 2.73 fold higher than intact trimethoprim.

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AUTHORS CONTRIBUTIONS

Conceptualization, E. Z. and L. F.; methodology, E. Z., L. F., H. F. and H. U., formal analysis, L. F., E. Z.,, H. U, and H. F.; resources, E. Z. and L. F.; writing—original draft preparation, L. F., E. Z. and H. F.; writing—review and editing, L. F., H. F., 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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