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IMPROVED SOLUBILITY NOVEL MULTICOMPONENT CRYSTALS OF FENOFIBRIC ACID-ACETYLSALISYLIC ACID

Deni Anggraini[1*], Gressy Novita[1], Intan Wulandari[1]
[1]*Sekolah Tinggi Ilmu Farmasi Riau, Pekanbaru Riau Indonesia*
**Email Corresponding: anggrainideni152@gmail.com*

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ABSTRACT

Solubility is an important physicochemical property of active pharmaceutical ingredients. Poor water solubility of active pharmaceutical ingredients leads to low bioavailability; therefore, efforts are needed to improve the solubility of active pharmaceutical ingredients. The goal of this study was to prepare and characterize novel multicomponent crystals of fenofibric acid (FA) using acid acetylsalicylic (ACE) as a coformer and to evaluate the solubility enhancement when prepared for multicomponent crystal formation. Solid characterization of the novel multicomponent crystals was performed using powder X-ray diffraction (XRD), differential scanning diffraction (DSC), Fourier transform infrared (FT-IR) spectroscopy, scanning electron microscopy (SEM), polarized microscopy, and solubility tests. Multicomponent crystals were prepared by the solvent drop grinding method using a few drops of an ethanol pro analyzer. The results showed that the solubility of multicomponent crystalline fenofibric acid was 4.7 times greater than that of pure fenofibric acid. Differential Scanning Calorimetry characterization results show the novel multicomponent crystals with a sharp endothermic peak at 136,65 ^{o}C. The PXRD diffractograms show no new diffraction peaks and a decrease in intensity. FT-IR spectroscopic analysis showed no new functional groups, and most of the transmittance peaks of the multicomponent crystals were superimposed between the peaks of fenofibric acid and acetylsalicylic acid. The novel multicomponent crystals fenofibric acid with acetylsalicylic acid as a coformer can improve the solubility of fenofibric acid

Keywords: Acetylsalicylic acid ; Fenofibric acid ; Multicomponent crystals ; Solubility

INTRODUCTION

Strategies to improve the physicochemical properties of active pharmaceutical ingredients (APIs) into new solids are a growing field that attracts the attention of academics and industry practitioners today. The exploration of new solid forms, such as amorphous, polymorphous, hydrates, solutions, salts, and cocrystals, has been widely carried out and has shown the different physicochemical properties of each solid form (Duggirala *et al.*, 2016).The exploration of solid crystal forms is popular and preferred. Among the new crystal forms, multicomponent crystal forms are more favored because most of the multicomponent crystal API are used to change solubility, tabletability, hygroscopicity, and chemical stability (Thakuria *et al.*, 2013)

Fenofibric acid (FA) in **Figure 1**, is an antihyperlipidemic drug that activates peroxisome proliferator-activated receptors (PPARs) and is the active form of fenofibrate (Kim *et al.*, 2015). FA is highly lipophilic (logP = 5.2), but low solubility in water (0.3 µg/mL at 37°C) (Granero, 2005). Based on the biowaiver classification, FA is a class II active pharmaceutical ingredient. Efforts have been made to increase the solubility of phenofibric acid so far, including the addition of an alkalizing agent $MgCO_3$, making a mixture of $MgCO_3$ in a 2:1 mol ratio (Kim *et al.*, 2016), the formation of a ternary solid dispersion of fenofibric acid with hyaluronic acid and polyethylene glycol (Yousaf *et al.*, 2019), formation of fenofibric acid salt using choline base, diethanolamine, trometamine, calcium, ethanolamine, and piperazine (Long *et al.*, 2007), surface solid dispersion using

croscarmellose sodium (Windriyati *et al.*, 2020), and formation of fenofibric acid self nanoemulsion to increase the dissolution rate (Suhery *et al.*, 2020).

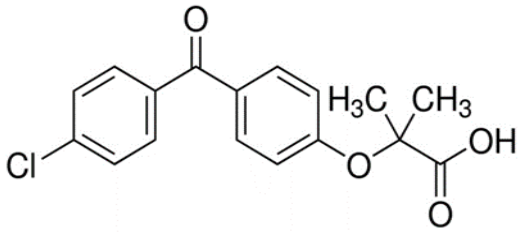

Figure 1. Molecule structure of fenofibric acid (National Center for Biotechnology Information, 2025).

Acetylsalicylic acid (ACE) in **Figure 2** is a water-soluble compound used as an analgesic, antipyretic, and nonsteroidal anti-inflammatory agent. At low doses, acetylsalicylic acid can inhibit platelet aggregation; therefore, it is used to prevent complications in atherosclerotic cardiovascular diseases, such as myocardial infarction and stroke (Brunton *et al.*, 2006). The coformers form multicomponent crystals. Coformers include food additives, preservatives, pharmaceutical excipients, and other active substances. The coformer groups consist of sugars, amino acids, carboxylic acids, and other groups (Karagianni *et al.*, 2018; Wathoni *et al.*, 2022). Coformers can also be drugs that work in line with the main medicinal ingredients. In this study, ACE was used as a coformer for multicomponent crystals of FA. In addition to being a coformer, ACE is an antiplatelet drug, so it is synergistic with FA as an antihyperlipidemic drug.

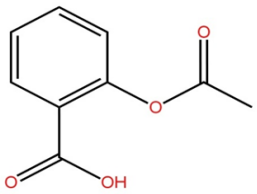

Figure 2. Molecule structure of acetylsalicylic acid (Depkes RI, 1995)

The aim of this study was to prepare novel multicomponent crystals of FA with ACE as coformer to improve the solubility of FA and conduct physicochemical characterization by DSC, FTIR, PXRD, SEM and polarization microscopy. in this study FA needs to improve its solubility because it is an antihyperlipidemia drug but has problems in solubility

RESEARCH METHODS

Equipment and Materials

Equipment used in the research are differential scanning calorimetry (Shimadzu DSC-60 Plus, Japan), Powder X-ray diffraction PANalytical PW 30/40 ((the Netherlands), FT-IR spectroscopy (Thermo scientific, USA), Scanning Electron Microscope (HITACHI FLEXSEM 1000, Japan), HPLC SHIMADZU (Japan) equipped with a DAD UV-Vis detector, Polarizing Microscope (Zeiss 700-Germany), orbital shaker (Heidolf Plug Germany).

The material used in this research was fenofibric acid (BOC Sciences, New York, USA). Acetylsalicylic acid was obtained from Tokyo Chemical Industry (Tokyo, Japan). acetonitrile and HPLC-grade ethanol (Merck, Darmstadt, Germany).

Research Procedure

Preparation FA-ACE Multicomponent Crystals

FA-ACE multicomponents were prepared using the solvent drop grinding method. First, FA (0.319 g, 1 mol) and acetylsalicylic acid (0.180 g; 1 mol) were accurately weighed and placed in a mortar. Then, 3 drops of ethanol were added and the mixture was crushed manually using a pestle. The multi-component crystals obtained were stored in a desiccator (Karagianni *et al.*, 2018)

Solid-State Characterization (Guo *et al.*, 2021)

a**.** Powder X-ray Diffraction Analysis

X-ray diffraction analysis was performed at room temperature on the FA, ACE, and FA-ACE multicomponent crystals. A Panalytical PW 30/40 X-ray diffractometer (The Netherlands) was used to measure an angle of 2 teta 5o - 40 °. The X-ray diffractometer was programmed as follows: target metal, Cu; filter, Kα; voltage, 45 kV; and current, 40 mA

b. Differential Scanning Calorimetry Analysis

Sample–5-7 mg (FA, ACE, and FA-ACE multicomponent crystals) was placed in a crucible (10 µL) using DSC (Shimadzu DSC-60 plus Japan). The Sample was heated and measured in the temperature range of 30 -250 ^{o}C heating rate of 10 ^{o}C per minute

c. Fourier Transform-Infrared Spectroscopy Analysis

Samples of 3-10 mg were mixed with KBr and compressed into pellets. The absorbance of the pellet was measured at 4000 cm-1 - 600 cm-1. Analysis was carried out on FA acid, ACE and FA-ACE multicomponent crystals.

d. Scanning Electron Microscopy Analysis

SEM analysis was performed to study the morphology of the crystals. The samples were characterized using a Scanning Electron Microscope (HITACHI FLEXSEM 1000, Japan) at an accelerating voltage of 10 kV. The samples were placed in a sample holder and sprayed with a thin gold-palladium film. The measurement conditions were set to 10 kV and 12 mA.

e. Polarizing Microscope Analysis

The contact method was performed using a polarizing microscope equipped with a hot stage. A quantity of FA powder (melting point 185.8 oC) was placed on the cover glass and heated until it melted and re-crystallized. ACE powder (melting point 143.7 oC) was placed on the side border of the cover glass. Reheat until all ACE melts and comes into contact with the FA crystal surface. The contact zone between the solid FA and ACE was observed under a polarizing microscope at 200 × magnification and recorded using a digital camera.

Solubility Test

FA and FA-ACE multicomponent crystals were weighed in excess amounts (equivalent to 25 mg FA) and dissolved in 100 ml distilled water. The mixture was stirred for 24 hours using an orbital shaker at room temperature (Yousaf *et al.* 2019). The amount of soluble FA was analyzed by HPLC (Shimadzu, Japan) with a DAD UV-Vis detector. HPLC system; Pursuit XRS C18 4.6×150 column. Mobile phase acetonitrile: water pH 3 (70:30). FA retention time 6.187 min. The experiments were performed in triplicate.

Data Analysis

The solubility data of the multicomponent crystals of fenofibric acid were compared with the solubility data of pure fenofibric acid and analyzed using the t-test. IR, DSC, and XRD characterization data were analyzed with the OriginLab application, and SEM test data were descriptively displayed in the form of images.

RESULTS AND DISCUSSION

Thermal analysis using differential scanning calorimetry is a fast and simple analytical method for determining the properties of crystals when a material is heated. This method can be used to characterize the thermodynamic properties of the solid phase and screen for the formation of multicomponent crystals (Yamashita *et al.*, 2013). The DSC test results (**Figure 3**) showed a sharp endothermic peak of FA at 185.84 ^{o}C which is the melting point of AF, while ACE showed an endothermic peak at 143.72 ^{o}C which is also the melting point of ACE. The 1:1 mole ratio FA- ACE multicomponent crystal shows a single endothermic peak at 136.65 ^{o}C where the melting point is lower than the melting point of the forming compound. The FA-ACE multicomponent crystal is a simple eutectic mixture, which is indicated by a single endothermic peak that is lower than that of the pure molecule (Dalal *et al.*, 2017). The melting point of the crystalline phase, which denotes intermolecular bonds in the crystal structure and lattice energy, affects the solubility of crystalline solids in water (Dwichandra Putra *et al.*, 2016), The lower the melting point, the less energy is needed to break the crystal lattice to dissolve, so the solubility of FA-ACE will be higher (Sopyan *et al.*, 2017).

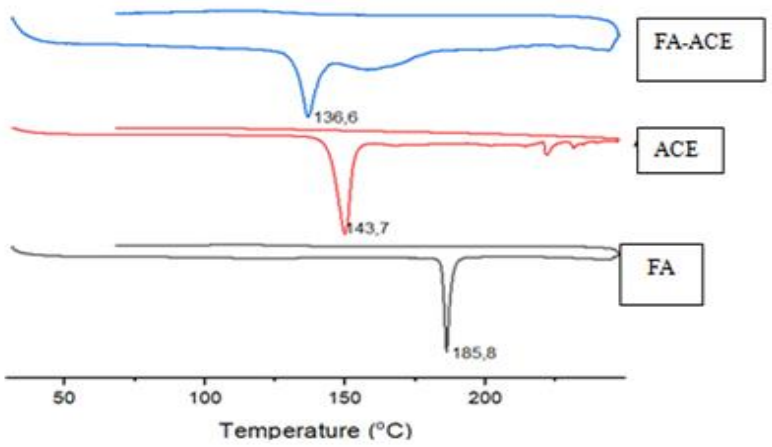

Figure 3. Overlay of differential scanning calorimetry thermogram of (A) FA (B) ACE and (C) the FA-ACE multicomponent crystals

PXRD analysis was used to evaluate the stability of the multicomponent crystals of FA, ACE coformer, and FA-ACE with a mole ratio of 1:1. The diffractogram (**Figure 4**) shows no new diffraction peaks, indicating that no new crystalline compounds were formed from the mixture. The FA diffractogram shows that the solid material had sharp diffraction peaks and a high degree of crystallinity. The FA diffraction peaks at the 2Ɵ angles of 18.64, 19.56, and 23.23. The decrease in intensity at the peak of the FA-ACE multicomponent crystal diffractogram at angle 2 Ɵ becomes 18,47, 19,01, and 23,15, which is the result of the reduction in the FA lattice or field after undergoing the crystallization process (Sopyan *et al.*, 2017).

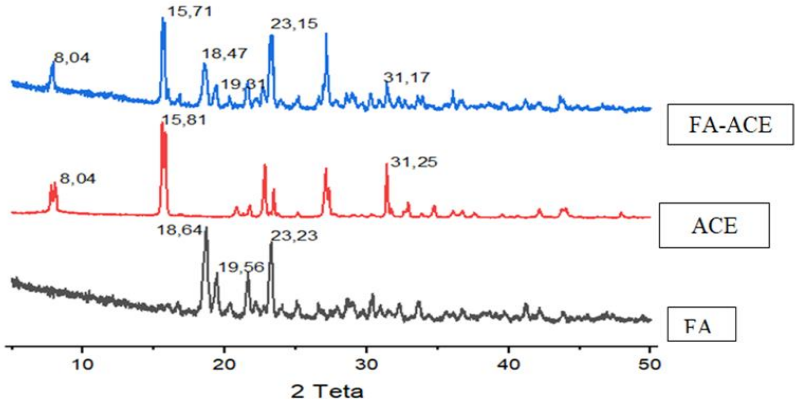

Figure 4. Overlay of powder X-ray diffraction patterns of FA, ACE, and FA-ACE multicomponent crystals.

Table I. Diffraction peaks and intensities of FA-ACE and FA

FA		FA-ACE	
Peak	Intensity	Peak	Intensity
18,64	9811	18,47	2680
19,81	5387	19,81	2464
23,23	8514	23,15	2984
TOTAL	23712		8128
% reduce	65,70%		

FTIR analysis was used to detect the molecular structure of compounds through functional group analysis by examining changes in the vibrations of the functional groups. FTIR spectroscopic analysis was performed on the FA, ACE, and FA-ACE multicomponent crystals (**Figure 5**). The spectrum of FA showed a broad peak at 2563 cm-1, which is the OH stretch of the carboxylic acid structure. In addition, the alkene functional group at 1698 cm-1 (C=O) and ether at 1277 cm-1 (C-O) peaks. The aromatic ring at 1591 cm-1 peak, vibration at 781 cm^{-1} is alkyl halide (C-Cl). The ACE spectrum showed a peak at 1746 cm^{-1}, indicating an ester functional group (C=O) and an O-H hydrogen bond of a carboxylic group at 2563 cm^{-1}. The functional group (C-H alkane) was found at 1466 cm^{-1}, and the aromatic ring was located at 1569 cm^{-1}. The FTIR spectrum of the FA-ACE multicomponent crystal is a combination of FA and ACE peaks. In the IR spectrum of the FA-ACE multicomponent crystal, there was no peak change or broadening, and there were no new or missing peaks. This indicates that AF and ACE do not chemically interact. Some studies have shown that slight changes in wave numbers indicate the presence of weak hydrogen bonds (Bazzo *et al.*, 2020).

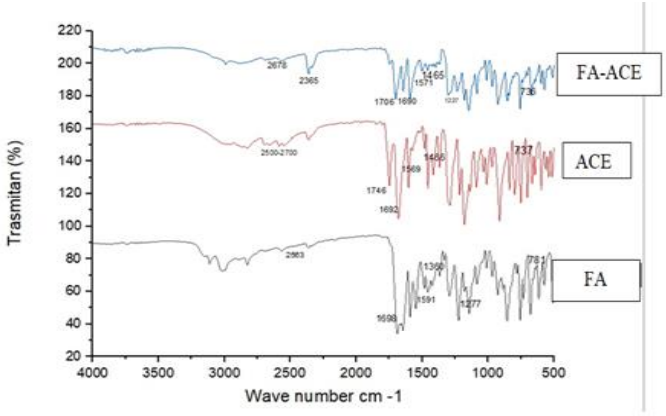

Figure 5. Overlay of fourier transform-infrared spectra of FA, ACE, and the FA-ACE multicomponent crystal

The SEM test results (**Figure 6**) show that there is an interaction between FA and the ACE coformer that can affect the crystal morphology of a substance. The crystal habit of pure FA is irregular cubic agglomerates with a sharp edge structure, and that of ACE is round oval with smooth edges. The FA-ACE crystal habit consists of long irregular crystals distributed as round oval crystals with smooth edges.

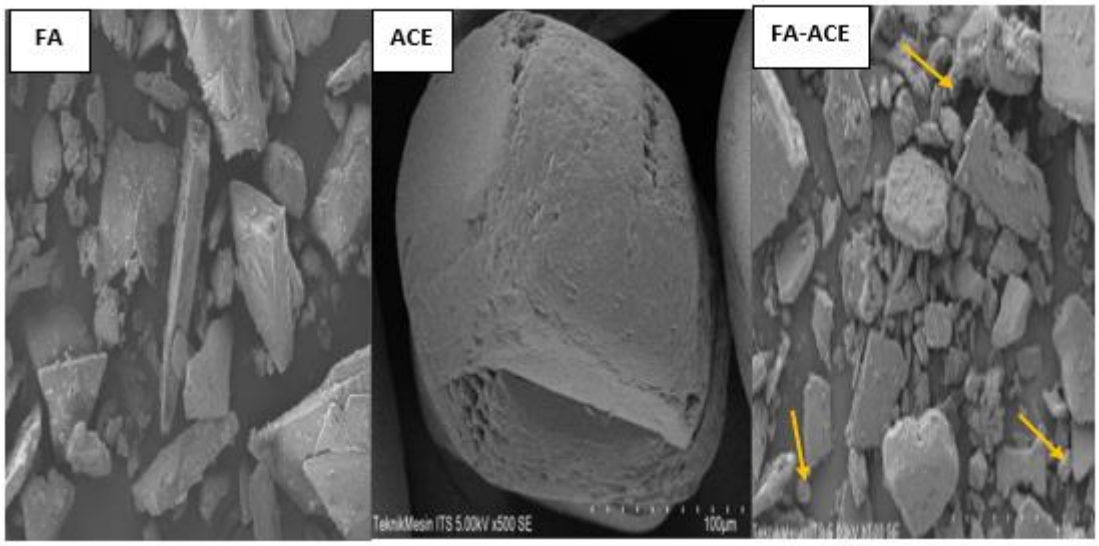

Figure 6. Scanning electron microphotographs of FA, ACE and the FA-ACE multicomponent crystal

Characterization tests by polarizing microscopy (**Figure 7**) showed the recrystallization of AF fused on side A, side C was the intermediate zone, and side B was the recrystallization of ACE fused. Both components exhibited a typical crystal habit. Side C is the contact zone between the AF solid and coformer. After recrystallization, the contact zone was black or empty, indicating the formation of a eutectic mixture (Patel *et al.*, 2019).

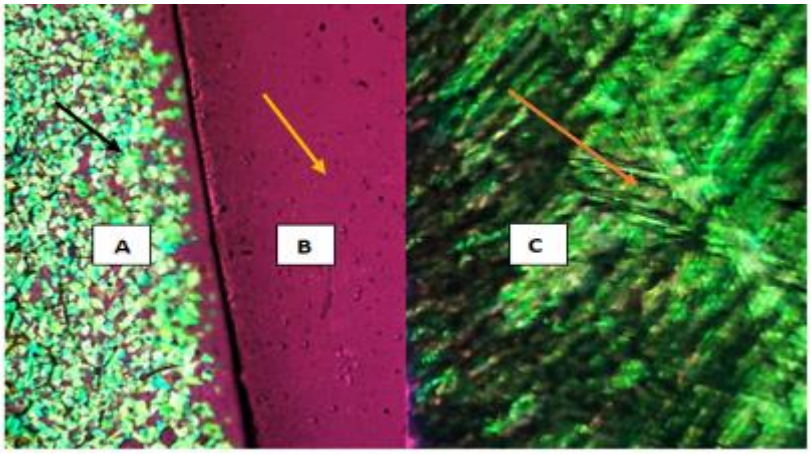

Figure 7. Polarizing microphoto (A) FA (B) contact zone between FA-ACE, and (C) ACE

The results of the solubility test of FA and the FA-ACE multicomponent crystal are presented in **Table I**. They indicated that the solubility of the FA-ACE multicomponent crystal was significantly higher (4,7-fold) than that of intact FA. The increased solubility of eutectic mixtures owing to reduced crystallinity results in a weakening of the crystal lattice energy. The crystal lattice energy affects the free energy of dissolution. The eutectic mixture melted at a lower temperature than the parent compound, resulting in lattice energy depletion and increased solubility (Chaturvedi *et al*. 2020).

Table II. Solubility of fenofibric acid (FA) and multicomponent crystal FA-ACE

Compound	Solubility (µg/mL)	± SD	Increased solubility
FA	88,16	0,07	0
FA-ACE	414,56	0,55	4,7 fold

Data were analyzed with an independent test with 95% confidence interval, n=6, P <0.05.

CONCLUSION

This study proved that the formation of FA multicomponent crystals with the ACE coformer was able to increase solubility by 4.7 times higher than pure phenofibric acid. The resulting solid was still a crystalline solid with a lower lattice energy. This multicomponent crystal formation method can improve the solubility and physicochemical properties of poorly soluble active pharmaceutical ingredients.

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