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COCRYSTAL FORMATION OF EFAVIRENZ-MALEIC ACID VIA ULTRASOUND-ASSISTED SOLUTION CO-CRYSTALLIZATION METHOD: CHARACTERIZATION AND MECHANICAL PROPERTY EVALUATION

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ABSTRACT

Efavirenz (EFV), a crucial drug for HIV infection, possesses unfavorable mechanical properties that complicate tablet production via direct compression. This study aimed to improve the mechanical properties, such as flowability and tabletability, of efavirenz (EFV) through co-crystal formation with maleic acid (MLT). The EFV-MLT co-crystal was prepared using the Ultrasound-assisted Solution Cocrystallization (USSC) method, employing distilled water as the solvent. To confirm its properties, the resultant co-crystal was characterized using polarizing microscopy, Powder X-ray Diffraction (PXRD), Differential Scanning Calorimetry (DSC), and Fourier-transform infrared (FTIR) spectroscopy. The mechanical properties of the co-crystals, including the compressibility index, Hausner ratio, tensile strength, and elastic recovery, were evaluated. Comprehensive characterization confirmed successful co-crystal formation using polarizing microscopy (revealing smaller needle-shaped crystals), PXRD (showing new diffraction peaks), DSC (indicating a lower melting point), and FTIR (demonstrating a wave shift). The findings of this study clearly demonstrate that the formation of EFV-MLT co-crystals via the USSC method significantly improves their mechanical properties compared with those of pure EFV.

Keywords: evafirenz, maleic acid, co-crystals, mechanical properties, USSC

INTRODUCTION

Efavirenz is a non-nucleoside reverse transcriptase inhibitor that is useful for treating human immunodeficiency virus type 1 (HIV-1) (Wang *et al*., 2019). Efavirenz is classified as a Class II drug in the Biopharmaceutical Classification System (BCS), characterized by poor solubility and good permeability (Da Costa *et al*., 2013). The recommended daily dosage of efavirenz is 600 mg, which is administered orally on an empty stomach, ideally at bedtime, to reduce the likelihood of potential neuropsychiatric side effects (Jaydip *et al*., 2020). Efavirenz possesses an extended plasma half-life, enabling once-daily administration (Vrouenraets *et al*., 2007).

The direct compression method could be a preferred choice because it provides the most brief, viable, and least complex way to create tablets. The manufacturer can mix an active substance with the excipient and lubricant, followed by compression, which makes it simple to prepare, and no extra handling steps are required (Pathan *et al*., 2024). The materials used in this method have good mechanical properties, such as compressibility and flow properties. Among the active substances with poor mechanical properties is efavirenz (EFV), which has poor compressibility and flowability. Some previous research that has been proven to enhance the mechanical properties of Efavirenz includes the formation of solid dispersion adsorbate (Mujtaba *et al*., 2025), as well as the formation of co-crystals with co formers such as lactic acid, adipic acid (Rajurkar *et al*., 2015) and fumaric acid (Gadade *et al*., 2018). Thus, to

prepare tablets with a high dose of active ingredients by direct compression, good mechanical properties, such as flowability and compressibility, are absolutely necessary.

The mechanical properties of a material are physical properties that describe its response to external forces. Superior compressibility, which is persistent and irreversible when the tension is removed, is typically exhibited by materials with stronger plasticity. The development of tablet formulations is hampered by the poor mechanical qualities of many organic substances. For organic materials, good tableting behavior predicts less elastic recovery and greater plastic deformation. Slip planes in crystal formations would facilitate plastic deformation and ultimately enhance the behavior of bulk compaction (Guo *et al*., 2021). By changing the crystal packing, cocrystallization has been shown to successfully enhance the mechanical qualities of active substance (Chaudhari *et al*., 2018).

The selection of coformers is also important in the crystallization process. Coformers are molecules that act as crystallizing agents. The coformers that can be used are substances that are acceptable for formulations, soluble in water, capable of forming noncovalent bonds, and contain functional groups that can create strong hydrogen bonds. Maleic acid (MLT), which has two carboxylic acid groups and is easily soluble in water, can be used as a coformer (Seragih, 2020). Therefore, the selection of coformers is crucial for crystallization.

Cocrystals are defined as single-phase crystalline, solid, homogeneous materials made up of at least two compounds present in a stoichiometric ratio: a drug and its corresponding coformer. Unlike salts, cocrystals are not primarily determined by ionic bonds in terms of the arrangement of compounds in the crystal lattice (Gowda *et al*., 2021). Pharmaceutical cocrystals have attracted attention because of their potential to modify a drug's physical characteristics, such as crystal structure, without affecting its pharmacological properties (Munaf *et al*., 2023). One of the significant advantages of cocrystals is their ability to change the mechanical qualities of active substances. Many drugs face issues such as poor compressibility and low stability, which can hamper their efficacy and manufacturability. These limitations can be mitigated by integrating cocrystals.

The USSC method (Ultrasound Assisted Solution Co-crystallization) can be used for co-crystal formation. The USSC method produces crystals using ultrasonic equipment from a solution or suspension of a drug mixture with a co-crystal former (CCF) (Kumar & Nanda, 2017). The crystal morphology produced by this method is more regular and uniform than that produced by the solvent grinding method (Alatas *et al*., 2022). Based on the above description, this study aimed to determine the influence of co-crystal formation of efavirenz and maleic acid using the USSC method on the improvement of mechanical properties, thus facilitating tablet production.

RESEARCH METHODS

Equipment and Materials

The equipments used in this research are analytical balance (Shimazu AP324X), Polarized Microscope (Olympus BX530) equipped with a camera, Powder X-ray Diffractometer (MiniFlex), Fourier Transform Infrared (Shimadzu IRAffinity-I Reflectance Diffuse-ORS8000), Differential Scanning Calorimetry (Shimadzu DSC-60Plus), ultrasonic shaker (Krisbow Ultrasonic), tap density tester (TSTF ZS-2E), granule flow tester (GFT100-AU), hardness tester (RWEK TBH125-series), hydraulic press (Athena).

The materials used in this study were efavirenz from PT. Kimia Farma Sungwun Pharmacopeia), maleic acid, distilled water, and other materials were used in the analysis.

Research Procedure

1. **Co-crystals Preparation with USSC Method**

   EFV and MLT were weighed in a molar ratio of 1:1, and distilled water was added and sonicated for 15 minutes. The solid mixture was observed under a polarized microscope until crystals were formed. The crystals formed were separated by filtration and dried at room temperature. The dry crystals were stored in a desiccator for evaluation (Alatas *et al*., 2022).

2. Co-crystals Characterization

Morphology Testing of Crystals

The crystals were visually and macroscopically observed using a polarizing microscope. Observations were conducted on the raw material EFV and the co-crystal product of EFV. Several samples were placed on a microscope slide, covered with a cover slip, and then observed under a polarized microscope.

Powder X-ray Diffraction

The X-ray diffraction patterns of pure EFV powder and pure MLT were determined. Recorded using an X-ray diffractometer with a Cu anode and graphite monochromator (γ = 1.5406Å). The samples were irradiated at a voltage of 40 Kv, current 30 Ma, and a 2θ range of 5 °to 45° with an increase of 2°C/minute.

FTIR Spectrum Analysis

Tests are conducted on EFV powder, MLT, and the co-crystal product using FTIR. Several samples were mixed with 200 mg of KBr. The samples were then measured with percent transmittance from a wavenumber of 400-4000 cm^{-1}.

Thermal Test (Differential Scanning Calorimetry)

The test was conducted on EFV and the co-crystal results were obtained using a Differential Scanning Calorimetry (DSC) instrument. It was calibrated for temperature and cell constant using indium metal. The sample (1-3 mg) was heated from 50 to 300°C at a heating rate of 10°C/min. The sample was continuously purged with nitrogen at a rate of 50 mL/min.

Flowability studies

Flowability and compressibility were determined by measuring the bulk density (ρb) and tapped density (ρt). The tapped and untapped powder volumes were used to define ρb and ρt, respectively ((USP-NF, 2023). The Compressibility index and Hausner ratio were calculated using Equations 1 and 2, respectively:

$$\text{Compressibility index} = \frac{\rho t - \rho b}{\rho t} \; x \; 100\ \% \qquad (1)$$

$$\text{Hausner ratio} = \frac{\rho t}{\rho b} \qquad (2)$$

Powder Compaction

Hydraulic press equipment (Athena) was used to compress tablets at a pressure of 10-50 kg/m^3 with a punch diameter of 11 mm; each tablet contained approximately 300 mg of pure EFV powder and EFV-MLT co-crystals obtained using the USSC method. Magnesium stearate was added as a lubricant for the compaction. The diameter and thickness of the compressed tablets were measured using a thickness gauge (Mitutoyo, Japan), while the tablet hardness was measured using a hardness tester (Erweka TBH125-series). The tablet diameter, tablet thickness, and breaking force data were used to determine the tensile strength (σ) according to Equation 3 (Shinebaum, 2021):

$$\sigma = \frac{2F}{\Pi dt} \qquad (3)$$

where F represents the breaking force (Newtons), d denotes the diameter of the tablet (mm), and t is the tablet thickness (mm).

Elastic recovery (ER) relies on the quantity of elastic energy accumulated during and post-compression, and it can be determined based on the diameters prior (Ho) and subsequent (H) to a 24-hour storage period, according to Equation 4 (Mohd Rosidi et al., 2021):

$$\%ER = \frac{(H - Ho)}{Ho} \; x \; 100 \qquad (4)$$

RESULTS AND DISCUSSION

The co-crystal formation of EFV-MLT was carried out using the Ultrasound Assisted Solution Cocrystallization (USSC) method. This method has advantages, such as producing smaller and finer particles and achieving supersaturation more easily. The co-crystal formation

process is affected by the cavitation energy generated by the ultrasonic waves. Cavitation energy can induce primary nucleation at lower levels of supersaturation, thereby reducing the induction time and the width of the metastable zone (Aher *et al*., 2013). Therefore, the USSC method was selected for large-scale co-crystal production. The co-crystal formation of EFV-MLT was conducted at a molar ratio of 1:1, using distilled water as the solvent. The reason for using Distilled water was used as the solvent because it can dissolve some of the EFV and MLT, thus accelerating crystallization. The resulting EFV-MLT co-crystals (1:1) were characterized using polarized microscopy, PXRD, DSC, and FTIR.

Polarization microscopy examination of the EFV, MLT, and EFV-MLT co-crystals (1:1) by the USSC method aimed to determine the differences in crystal habits. Testing with a polarizing microscope equipped with a camera is one way to visually confirm the formation of co-crystals. The EFV-MLT co-crystals (1:1) were characterized under a polarization microscope by adding a small amount of liquid paraffin to make the formed crystals more visible. As shown in **Figure 1**, the crystal habit of EFV was needle-shaped, whereas that of MLT was rhombohedral. Meanwhile, the EFV-MLT co-crystals (1:1) showed a smaller crystal habit compared to its starting component forms and had a different habit from MLT, which was needle-like. This change in crystal habit is one piece of evidence that the co-crystal EFV-MLT has been formed.

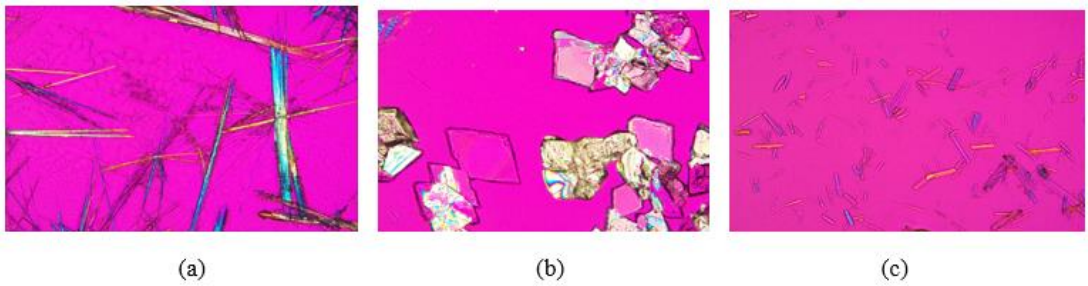

Figure 1. Crystal morphology of (a) EFV (b) MLT and (c) EFV-MLT - USSC result (1:1) with 200 x magnification images under a polarizing microscope

PXRD is a dependable method for determining the formation of new solid phases. The results of this characterization are presented as a diffractogram. The formation of co-crystals is marked by the disappearance of old diffraction peaks and the presence of new diffraction peaks that are characteristic of the forming substance (Holder & Schaak, 2019). The PXRD patterns of EFV, MLT, and EFV-MLT co-crystals obtained using the USSC method are shown in **Figure 2**. EFV exhibited distinctive crystalline peaks at 2θ values of 6.23°, 12.51°, 14.39°, 16.92°, 20.39°, 25.12°, 28.26 °, and 32.98°, whereas MLT exhibited distinctive crystalline peaks at 2θ values of 17.87°, 22.59°, 28.26°, 38.65 and 40.87°. The primary peaks of the EFV-MLT co-crystals (1:1) are located at 2θ with values of 6.53, 12.20, 16.92, 17.56, 21.34, 22.90, 25.73, 29.51, 38.04 and 58.18°. The changes in the diffractogram, indicated by the loss of diffraction peaks and the appearance of new diffraction peaks, signify that a co-crystal has formed.

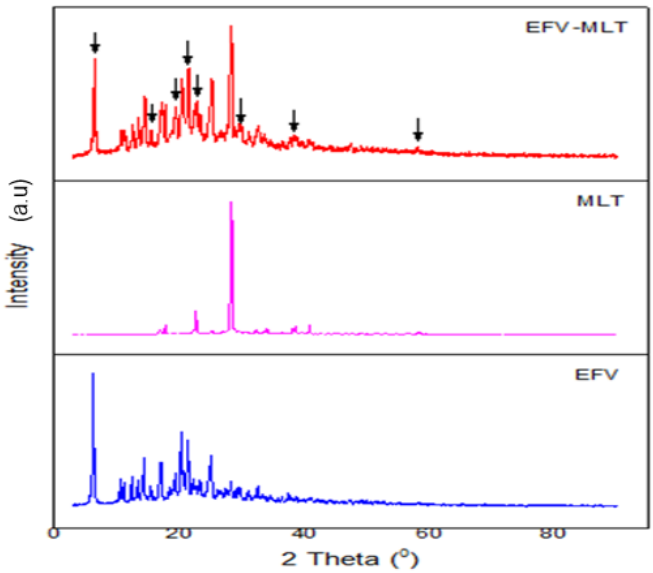

Figure 2. ***PXRD diffractograms of the EFV-MLT-USSC results were compared those with of the starting components.***

Differential Scanning Calorimetry (DSC) was conducted on EFV, MLT and EFV-MLT co-crystals (1:1). This analysis was used to characterize the co-crystal by examining the changes in thermodynamic properties that occur when the co-crystal receives thermal energy (Putri *et al*., 2023). The formation of co-crystals is marked by the presence of a melting point below or between the two constituent compounds. The thermogram in **Figure 3** shows the DSC test results for EFV and MLT melting at 133.23 °C and 176.36 °C, respectively. Meanwhile, the EFV-MLT co-crystals (1:1) melted at 113.34 °C. The melting point of the co-crystal, which was lower than those of EFV and MLT, indicated that the co-crystal was successfully formed.

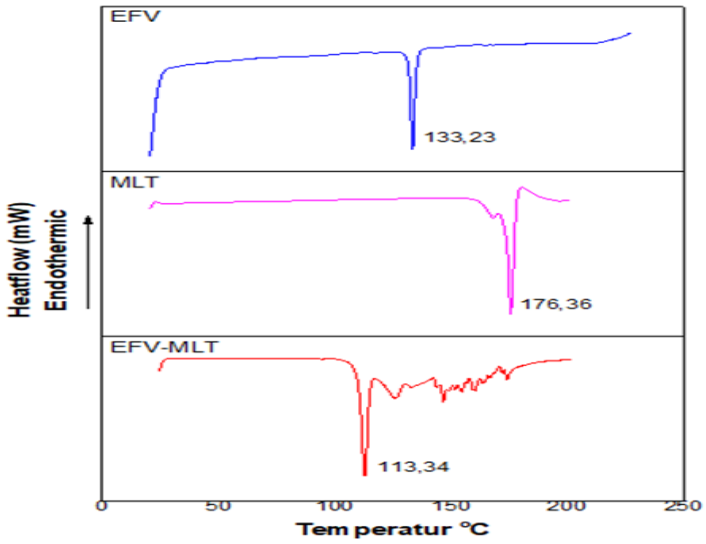

Figure 3. ***DSC thermograms of the EFV-MLT-USSC results compared to the starting components.***

Fourier Transform Infrared (FTIR) spectroscopy was used to determine the formation of co-crystals by examining the changes in functional groups due to intermolecular interactions (Hiendrawan *et al*., 2016). The**Figure *4*** infrared spectrum was produced from the graph of

percentage transmittance against infrared wave numbers, as shown in Figure 4. Based on the results obtained, EFV shows peaks at wave numbers 3310.66, 3048.21, 2940.98, 1755.33, 1620.53, 1515.28, and 2227.14 cm^{-1}, which corresponded to -OH stretch, aliphatic –CH stretch, aromatic –CH stretch, C=O stretch, C=N stretch, aliphatic C=C stretch, and C≡N stretch, while MLT shows peaks at wave numbers 3735.50, 3075.78, 2954.25, 1701.20, and 2360.92 cm^{-1}, indicating the OH stretch group, aliphatic –CH stretch, aromatic –CH stretch, C=O stretch, and C≡N stretch, respectively. The interaction between molecules that primarily occurs during the formation of co-crystals is hydrogen bonding. A shift in the wavenumber occurs when hydrogen bonds form between the active and coformers.

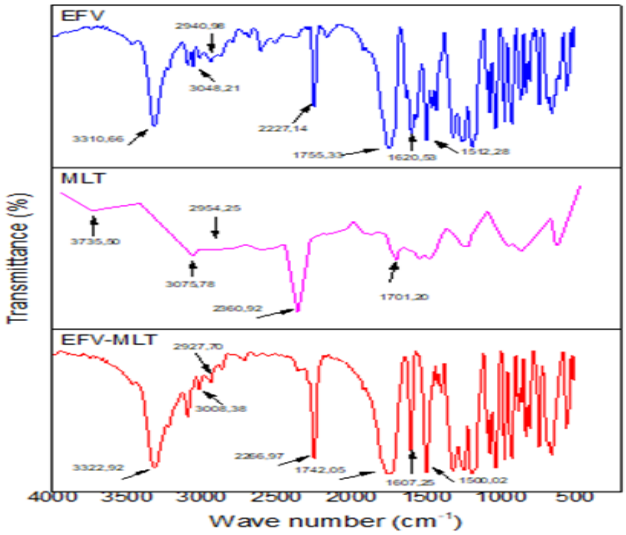

Figure 4. FTIR spectra of EFV-MLT- USSC result compared to the starting components.

Compressibility testing, expressed as a percentage, was conducted to determine whether a certain substance can be broken down and transformed into a solid mass under pressure (Hart, 2015). From the results of the compressibility test, the values of EFV and the EFV-MLT co-crystals (1:1) were 27.666±1.662 and 14.099±1.778, respectively. The flow characteristics of a powder increase as the value of the compaction index decreases (Permatasari *et al.*, 2016).

Table I. Flowability of EFV and EFV-MLT co-crystals.

Sample	Bulk Density	Tapped Density	Carr Index (%)	Hausner Ratio	Flow Properties
EFV	0.571±0	0.790±0.0018	27.666±1.662	1.383±0.032	Poor
EFV-MLT	0.606±0	0.706±0.0118	14.099±1.778	1.164±0.019	Good

Tabletability refers to the ability of a substance to transform into tablet form with a certain strength under the influence of compression pressure (Yaddalapudi *et al*., 2014). The tabletability of a tablet can be assessed by its tensile strength and elastic recovery. During tablet manufacturing, the powder undergoes plastic and elastic deformations. A good tablet has a high tensile strength and plasticity (Yu *et al*., 2020). A low tensile strength indicates that the powder has a high elastic recovery, and the resulting tablet will experience capping (Persson *et al*., 2018). The data from the tensile strength testing of the EFV and EFV-MLT co-crystals (1:1) are shown in **Figure 5**. The compression of EFV tablets was carried out at several pressure variations, namely, 10, 20, 30, 40, and 50 kg/cm^2. However, pure EFV was formed only at a pressure of 10 kg/cm^2. When removed from the mold, the tablet had already

experienced capping, making further testing impossible. Meanwhile, the EFV-MLT co-crystals (1:1) could only be compressed into tablets at a pressure of 40 kg/cm². The higher tensile strength compared to pure EFV indicates that the EFV–MLT co-crystals (1:1) exhibited better powder compaction capability. Smaller particles have a better ability to compress powder than larger particles because they have more bonds and a larger surface area (Yohannes *et al*., 2018). However, there are also opinions that tablets that can be well-formed at the production scale must have a minimum tensile strength of 2 Mpa (Ratih *et al.*, 2020). Thus, although the tensile strength obtained from the EFV-MLT co-crystals (1:1) increased, it still did not meet the minimum requirements for production.

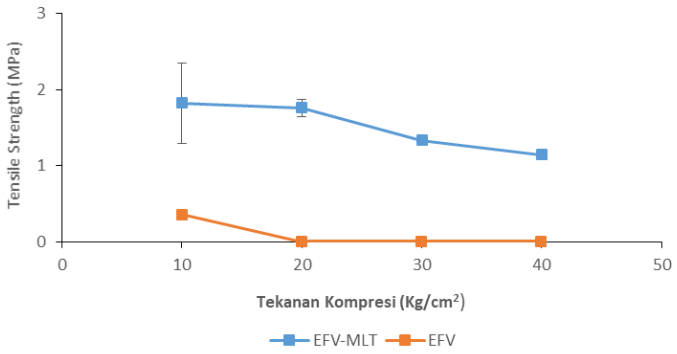

Figure 5. ***Tabletability profiles of pure EFV and EFV-MLT cocrystals.***

Elastic recovery pertains to the total elastic energy that is stored and subsequently released during compression. A high % elastic recovery value during compression indicates poor plasticity. Low plasticity suggests poor compaction properties because bonding areas after compaction are difficult to form, leading to tablet brittleness (Aher *et al.*, 2013). The purpose of this test was to determine whether there was a change in the tablets during a 24-hour storage period. The % elastic recovery results are shown in **Figure 6**. The value for the EFV-MLT co-crystals (1:1) was lower than that for pure EFV, indicating that the co-crystal tablet had more plastic properties than the pure substance.

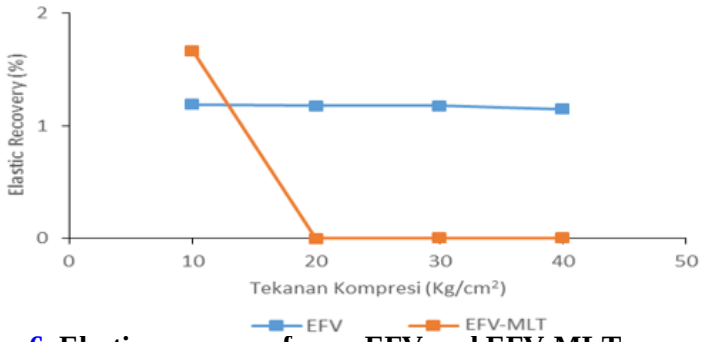

Figure 6. Elastic recovery of pure EFV and EFV-MLT co-crystals.

CONCLUSION

Co-crystal formation of efavirenz (EFV) with a co-former derivative of carboxylic acid, namely Maleic Acid (MLT), was achieved using the ultrasound-assisted solution cocrystallization (USSC) method at a molar ratio of 1:1 with distilled water as the solvent, indicating the formation of EFV-MLT co-crystals. This study is supported by the characterization data of the co-crystals using polarization microscopy, Differential Scanning Calorimetry (DSC), Powder X-ray Diffraction (PXRD), and Fourier-transform infrared (FTIR) spectroscopy. The mechanical properties of the co-crystals include the compressibility index, Husner ratio, tensile strength, and elastic recovery. The findings of this study indicate

that the formation of co-crystals between EFV and MLT results in improved mechanical properties compared to those of pure EFV.

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