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RESEARCH ARTICLE

Fluconazole-tartaric acid co-crystal formation and its mechanical properties

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Abstract

Introduction: The formation of co-crystal is widely studied to obtain more favourable physicochemical properties than the pure active pharmaceutical ingredient (API). The co-crystal formation between an anti-fungal drug, fluconazole (FLU), and tartaric acid (TAR) has been investigated and its impact on mechanical properties has also been studied. **Methods:** The co-crystal of FLU-TAR (1:1) molar ratio was prepared by ultrasound-assisted solution co-crystallization (USSC) method with ethanol as the solvent. Polarization microscopy was used to observe the crystal morphology. Meanwhile, powder X-ray diffraction (PXRD) and differential scanning calorimetry (DSC) methods were used to characterise the co-crystal formation. The mechanical properties of the co-crystal, such as flowability and tabletability, were compared with pure FLU. **Results:** Photomicroscopes revealed the unique crystal morphology of the USSC product was different from the two starting components. The typical PXRD pattern was shown by the USSC product, which indicated the formation of FLU-TAR co-crystal. In addition, the DSC thermogram revealed 169.2°C as the melting point of the FLU-TAR co-crystal, which is between the melting points of FLU and TAR. It indicates that FLU-TAR co-crystal has better flowability and tabletability than pure FLU. **Conclusion:** FLU-TAR co-crystal is one of the alternative solid forms for a raw material in pharmaceutical tablet preparation because it has better mechanical properties than pure fluconazole.

Introduction

Currently, more than 70.0% of active pharmaceutical ingredients (APIs) are given in tablet dosage form since this form is stable and easy to use. Today, the direct compress method is widely used for the tablet manufacturing process as it is fast and it requires little equipment and personnel (Maghsoodi, 2012). However, tablet manufacturing that employs this method requires good mechanical properties of API, such as flowability and tabletability.

Modification of the crystal structure of an API due to different polymorphs can change the mechanical properties of an active pharmaceutical ingredient (API) (Upadhyay *et al*., 2013; Guadalupe Sánchez-González *et al.*, 2015; Yin *et al.,* 2016). To obtain polymorphic modifications from an API, however, is not easy. Sometimes, the polymorphic modification of an API is obtained accidentally from an experiment. Also, some of the polymorphic modifications obtained are less stable and could change to the more stable modifications during storage. One of the crystal engineering techniques that can be employed intentionally to obtain beneficial physicochemical properties is the formation of co-crystals.

Co-crystals are formed due to the presence of non-covalent bonds, including hydrogen bonds between an API and an excipient, which is also solid in the specific

stoichiometric ratio (Pan *et al.*, 2017). The co-crystal formation has a fascinating method. Apart from being able to increase solubility, dissolution rate, and bioavailability, it also can improve mechanical properties. Previous studies have succeeded in obtaining co-crystals that can improve the mechanical properties of APIs, including paracetamol (Kiarki *et al.*, 2009; Ahmed, Shimpi, & Velaga, 2016; Hiendrawan *et al.*, 2016), flufenamic acid (Joshi *et al.,* 2018), and telmisartan (Ratih *et al.*, 2018).

Fluconazole (FLU) is a bis-triazole derivative in the treatment of candidiasis and cryptococcal meningitis. The drug is given orally in capsule or tablet dosage form (Charoo *et al.*, 2014). However, FLU has poor flowability, so this drug has limitations in the manufacture of tablets by direct compression (Consiglieri *et al.*, 2010). Several fluconazole co-crystals have been made, but they are generally made to increase their solubility, including fluconazole co-crystals with malic acid, maleic acid, fumaric acid (Kastelic et al., 2010), dipicolinic acid, and adipic acid (Dayo Owoyemi *et al*., 2019). However, after a thorough search of the relevant literature, it was revealed that a study on the mechanical properties of fluconazole co-crystals is yet to be published. Therefore, the purpose of this study is to prepare fluconazole co-crystal with tartaric acid (TAR) as the co-former and investigates its impact on mechanical properties. Based on the chemical structure of the two components, both have a great potential to form a co-crystal. The chances of hydrogen bonding occur between the triazole group of fluconazole and the carboxylic group of tartaric acid.

Material and method

Material

Fluconazole was obtained from Viruphaksa, Hyderabad, India, while dl-tartaric acid and ethanol were purchased from Merck, Indonesia.

Preparation of Fluconazole-TAR (FLU-TAR) co-crystal

Fluconazole-tartaric acid co-crystal (FLU-TAR) was produced by the ultrasound-assisted solution co-crystallisation (USSC) method. A mixture of 3.06 g of fluconazole (10 mmol) and 1.5 g of dl-tartaric acid (10 mmol) was put into an Erlenmeyer flask and dispersed in 40 mL ethanol. The Erlenmeyer flask was placed on Branson ultrasonic 3510-DTH and was operated at 40-45^{o}C and a frequency of 42 kHz. After 20 minutes, the Erlenmeyer flask was removed from the ultrasonic and left for five minutes at room temperature. The habit crystal of the solid from the Erlenmeyer flask was observed to ensure that FLU-TAR co-crystal had been produced. Then, the solid was separated by filtration and dried at room temperature. Afterwards, the dried solid was stored in a desiccator.

Characterisation of FLU-TAR Co-crystal formation by polarization microscopy

The dried solid from the USSC product was placed on a closed slide, and the crystal morphology was observed under an Olympus BX-53 polarizing microscope. The photomicroscopes were taken using a digital camera (Optilab Advanced Plus) integrated into a polarizing microscope. The crystal morphology of the USSC product was compared with the crystal morphology of the recrystallised pure FLU and TAR in ethanol solvent.

Characterisation of FLU-TAR Co-crystal formation by Powder X-ray Diffraction (PXRD)

The powder X-ray diffraction pattern was determined for USSC products, pure FLU, and TAR. The data collection of powder X-ray diffraction pattern was carried out using the Panalytical Empyrean XRD system operated at 40 kV of generator voltage and 30 mA of generator current. The sample scanning speed was set at 2°/min with a measurement range of five to 45° of 20 angles.

Characterisation of FLU-TAR Co-crystal formation by Differential Scanning Calorimetry (DSC)

A total of three to five mg of dried solid from the USSC product was placed on an aluminium pan, and the DSC thermogram was recorded on the DSC-60 plus (Shimadzu, Japan). The heating rate was set at 10°/min and range from 30 to 200°C under nitrogen flow with a flow rate of 20 mL/min. DSC measurements were also carried out on pure FLU and TAR.

Evaluation of angle of repose and powder flow rate

Each of 20 g of pure FLU and FLU-TAR co-crystal was put into a funnel and left until all the powder flows and falls on a flat surface. The height (h) and radius (r) of the conical pile of powder were measured, and the angle of repose (θ) was calculated using equation 1.

$$Tg\ \theta = h/r \quad \text{(Equation 1)}$$

Flowability study

Carr's compressibility index and Hausner's ratio were calculated based on the values obtained from the determination of bulk density (ρ_b) and tapped density (ρ_t). The determination of bulk and tapped density was conducted using an automatic tapped density tester (ZS-2E Tapped Density Tester, China). Each 20 g of pure FLU and FLU-TAR co-crystal was placed in the cylinder

of the tapped density tester, and its volume (v_b) was recorded. Afterwards, a total of 500 beats were performed on each powder until the volume did not change and the volume was recorded (v_t). The bulk density, tapped density, Carr's compressibility index, and Hausner's ratio were calculated based on equations 2, 3, 4, and 5, respectively (Kaialy *et al.*, 2012b).

$$\rho_b = m/v_b \quad \text{(Equation 2)}$$

$$\rho_t = m/v_t \quad \text{(Equation 3)}$$

$$\text{Carr's compressibility index} = \rho_b/\rho_t \quad \text{(Equation 4)}$$

$$\text{Hausner's ratio} = (\rho_t-\rho_b)/\rho_t \quad \text{(Equation 5)}$$

Tabletability study

Tabletability studies were carried out by determining the tensile strength and elastic recovery percentage of and pure FLU and FLU-TAR co-crystal. Powder compaction was performed using the Athena manual hydraulic press (Athena Technology, India) and 11 mm-flat round tools (punch and die). The die was filled with 300 mg of powder and compressed into a tablet at ten to 60 kg/cm^2 of the pressure range. Every time the compaction process was performed, the punch and die were coated with 2% (w/w) magnesium stearate in ethanol. The diameter, thickness, and hardness of tablets were measured as soon as the tablet was ejected from the die hole. The tablets were allowed for 24 hours, and the diameter was measured again. A digital calliper was used to measure the diameter and thickness of tablets. The tablet's hardness was measured by the TBH-125 series hardness tester (Erweka, Germany). Tensile strength (σ) was calculated based on the values of diameter (D), thickness (T), and braking force (F) according to equation 6 (Kawashima *et al.*, 1994). The elastic recovery (ER) percentage was calculated based on the initial diameter (D_0) and the diameter after the tablet was stored for 24 hours (D) according to Equation 7. The appearance of the tablet was also observed after being stored for 24 hours.

$$\text{Tensile strength } (\sigma) = 2F/\pi DT \quad \text{(Equation 6)}$$

$$\text{Elastic recovery percentage } (\%ER) = (D- D_0)/D \quad \text{(Equation 7)}$$

Results

Polarisation microscopy

Photomicroscopes of USSC product and recrystallization results in ethanol of the two constituent components are shown in Figure 1. The crystal habit of dry solid from the USSC product was a plate-like crystal (tabular habit). The pure FLU and TAR crystal habits were needle-like crystals (acicular habit) and prism-like crystals (prismatic habit), respectively.

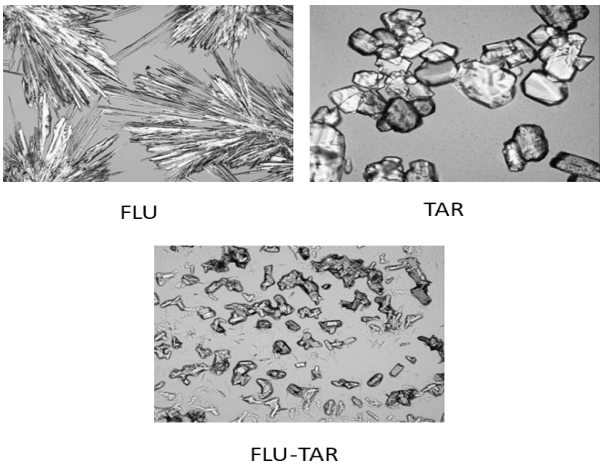

Figure 1: Crystal morphology of FLU, TAR, and FLU-TAR USSC product

Powder X-ray diffraction patterns

Figure 2 demonstrates the PXRD patterns of the FLU, TAR, and USSC products. PXRD pattern of the USSC product of FLU-TAR has typical peaks as indicated by the arrows at angles of 2θ = 7.7, 11.1, 16.5, 16.9, 17.6, 17.9, 19.1, 19.9, 22.1, 22.5, 23.2, and 24.0°.

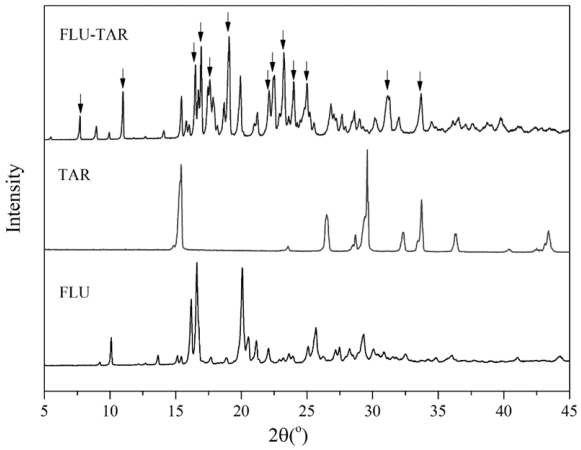

Figure 2: Powder X-ray diffraction patterns of FLU, TAR, and FLU-TAR co-crystal

Differential Scanning Calorimetry (DSC) thermograms

Figure 3 shows the DSC thermograms of FLU, TAR, and the FLU-TAR USSC products. The DSC thermogram of FLU showed two endothermic peaks (102.40 and 140.25°C), whilst the DSC thermogram of TAR revealed an endothermic peak at 173.17°C. The USSC product has an endothermic peak at 165.92°C.

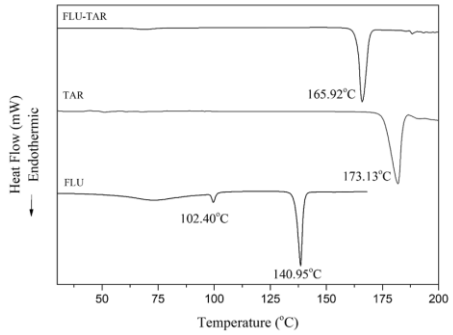

Figure 3: Differential scanning calorimetry thermograms of FLU, TAR, and FLU-TAR co-crystal

The angle of repose evaluation

The angle of repose of pure FLU and FLU-TAR co-crystal were 41.69±0.25 and 34.16±0.54, respectively.

Flowability study

The bulk density, tapped density, Carr's compressibility index, and Hausner's ratio of pure FLU and FLU-TAR co-crystal are shown in Table I.

Tabletability study

Figure 4 shows the tensile strength profile of pure FLU and FLU-TAR co-crystal at ten to 60 kg/cm^2 of compression pressure range, whilst both elastic recovery profile is shown in Figure 5. The appearance of pure FLU and FLU-TAR co-crystal tablets after being compressed at a compaction pressure of 50 kg/cm^2 is shown in Figure 6.

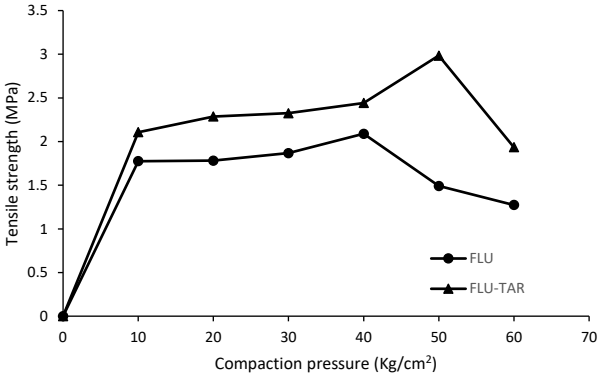

Figure 4: Tabletability profiles of FLU and FLU-TAR co-crystal

Table I: Flowability of FLU and FLU-TAR Co-crystal

Materials	Bulk density	Tapped density	Carr's compressibility index (%)	Hausner's ratio	Flow properties
FLU	0.505±0.005	0.726±0.010	30.2±0.20	1.437±0.007	Poor
FLU-TAR	0.469±0.013	0.545±0.017	14.1±0.32	1.163±0.004	Good

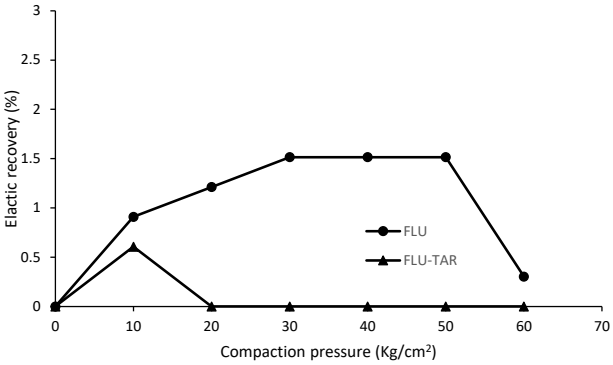

Figure 5: The elastic recovery of FLU and FLU-TAR co-crystal

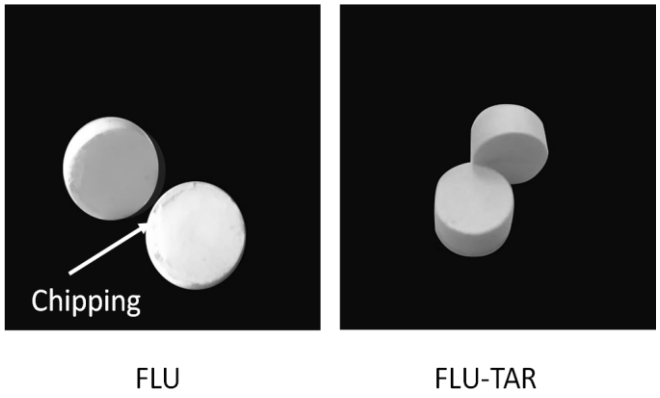

Figure 6: Appearance of FLU and FLU-TAR co-crystal tablets at 50 kg/cm^2 of compaction pressure

Discussion

The USSC method was employed to prepare FLU-TAR co-crystal since this method has a good effect on the scale-up process of co-crystal. Therefore, it can be applied to large-scale production processes. This method also has several advantages, namely the relatively short manufacturing time, the slow crystallization process that can produce a more regular crystal packing, less solvent is used, and compared to the grinding method, this method avoids crystal defects caused by the grinding process. In addition. the USSC method produces more uniform particles than any grinding method because the nucleation of co-crystal at low supersaturation in a solution occurs influenced by the presence of ultrasonic wave cavitation energy (Aher *et al.*, 2010; Zeng *et al.*, 2014). The solvent can only partially dissolve both the active substance and co-former to prevent each component from crystallizing individually as the solution is always in supersaturation (Thakuria *et al.*, 2013). Using the appropriate type and volume of solvent in the USSC method will produce a uniform and fine co-crystal form. In this study, ethanol was selected as a solvent in the co-crystal preparation as it fulfils all the criteria as a proper solvent in produce the FLU-TAR co-crystal where two components are soluble in this solvent.

Observation of crystal morphology using a polarizing microscope was conducted to identify the formation of FLU-TAR co-crystal using the USSC method. In the co-crystal formation process using the USSC method, the two constituent components (FLU and TAR) were converted into FLU-TAR co-crystal. This change can be known by observing the differences in the crystal habit of each of its constituent components with the habit crystal after the process was stopped. This difference in crystal morphology may indicate a change in solid form during the manufacturing process using the USSC method due to the intermolecular interaction between FLU and TAR.

PXRD is a reliable method to determine the interaction between two solid components that form a co-crystal by observing the difference in the PXRD pattern between the manufactured product and the respective solid components. The main peaks differ from the main peaks found in pure FLU and TAR, and this may reveal an interaction between the two solid components to establish a FLU-TAR co-crystal.

Differential Scanning Calorimetry (DSC) is a thermal analysis used to confirm the co-crystal formation since this method can show the thermal behaviour of a solid form, including changes in melting point. The DSC thermogram of FLU showed two endothermic peaks, one at 102.40°C due to dehydration of a water molecule from fluconazole monohydrate and another at 140.25°C in consequence of its melting point (Alkhamis, Obaidat, & Nuseirat, 2002). A typical endothermic at 173.17°C on the DSC thermogram of TAR is related to its melting point. Different from the thermal behaviour of the pure FLU and TAR, the DSC thermogram of the FLU-TAR USSC product showed no endothermic peaks at the melting temperatures of the two components. However, there was only one sharp endothermic peak located between the melting points of FLU and TAR at 165.92ºC. This thermal behaviour confirms that there was intermolecular interaction between FLU and TAR to produce FLU-TAR co-crystal. The sharp endothermic peak at 165.92ºC is related to the melting point of FLU-TAR co-crystal. The melting point below or between the melting points of the two initial components could indicate the formation of co-crystal (Batisai *et al.*, 2014).

The angles of repose of the pure FLU and the FLU-TAR co-crystal were 41.69±0.25° and 34.16±0.54°, respectively. It was found that FLU-TAR co-crystal had a better angle of repose than pure FLU. The angle of repose of FLU is in the poor flow category (46-55°), while the co-crystal FLU-TAR is in the passable or moderate flow category (36-40°) (Satpute & Tour, 2013).

It is crucial to know the mechanical properties of an API because it can be a consideration in determining the method used in the tablet manufacturing process. Flowability and tabletability are the mechanical properties, which are generally used as the basis for selecting methods in the tablet manufacturing process. The tablet manufacturing process by direct compress method requires good flowability and tabletability from an API. In this case, flowability is an important parameter in the manufacture of a pharmaceutical tablet. On the other hand, compressibility is the ability of a material to reduce the volume due to the pressure applied (Sun & Grant, 2001). Carr's compressibility index and Hausner's ratio could reveal the flowability of the powder. The flowability study shows the Carr's compressibility index of the FLU-TAR co-crystal is in the good flowability category (eight to 16%) while Carr's compressibility index of pure FLU is in a bad category (23-35%) (Satpute & Tour, 2013). The high Carr's compressibility index of pure FLU might be due to its needle-shaped crystal morphology that allows the aggregation of powders arising from the high mechanical forces interlocking. Conversely, a decrease in Carr's compressibility index of FLU-TAR co-crystal was caused by its tabular-shaped crystal habit that allows a decrease in the relative contact area between particles so that its cohesion properties decrease and result in less physical contact (Kaialy *et al.*, 2012a). Similar to Carr's compressibility index, based on the value of Hausner's ratio, the FLU-TAR co-crystal is also in the good flowability category (1.12-1.18), while pure FLU is in the poor flowability category (1.35-1.45).

The tabletability is defined as the ability of a powder or particle to be converted into a tablet with a certain strength under compaction pressure (Jain, Khomane, & Bansal, 2014; Tye, Sun, & Amidon, 2005). The tabletability profiles (tensile strength versus compaction pressure) of pure FLU and FLU-TAR co-crystal were measured in a compaction pressure range of ten to 60 kg/cm^2. The tabletability profile demonstrated pure FLU could be compressed to a compaction pressure of 60 kg/cm^2. However, the appearance of the tablet showed chipping at compaction pressures above 40 kg/cm^2. This condition is due to the needle-shaped crystal habit of FLU that has poor flowability with high electrostatic energy. This needle-shaped crystal habit has high internal friction, which causes a lot of space in the tablet mould that is not filled during the compaction process (Kaialy *et al.*, 2014). Conversely, FLU-TAR co-crystal can form a tablet without chipping under compaction pressures. FLU-TAR co-crystal has a higher tensile strength value compared to pure FLU, which indicates that FLU-TAR co-crystal tabletability is better than pure FLU. The tabletability profile showed that at a compaction pressure of 10 kg/cm^2, the FLU-TAR co-crystal has a tensile strength value of 2.108 MPa. The tensile strength increased steadily until a compaction pressure of 50 kg/cm^2 with a tensile strength value of 2.984 MPa, which is the maximum point of compaction or called the breaking point. After this point has passed, a material undergoes extensive fragmentation, which is called a brittle fracture (Jain *et al*., 2014). The tabletability profiles showed differences in the FLU and FLU-TAR co-crystal breakpoints. The tensile strength value of the FLU-TAR co-crystal was higher than that of FLU, and this indicates that the FLU-TAR co-crystal has better plasticity than pure FLU. To produce a good tablet, the tensile strength should be at least 2 MPa (Perumalla & Sun, 2014). With tensile strength values above 2 MPa, the FLU-TAR co-crystal should not encounter problems in the tablet manufacturing process by the direct compress method.

The percentage of elastic recovery can indicate the elasticity of various pharmaceutical materials to be compressed into tablets. The risk of capping or other defects during tablet development and manufacture can be overcome by testing the elastic recovery percentage of active pharmaceutical ingredients or excipients. The percentage of elastic recovery of the pure FLU is higher than that of the FLU-TAR co-crystal, and it indicates that the FLU-TAR co-crystal has better tabletability than a pure FLU. The more plastic powders can form, the greater the permanent bonds between particles after the compaction process, so they can show good tabletability (Chattoraj *et al.*, 2014). The properties of plastic and elastic deformation determine the ability of a material to be compressed. Particle rearrangement and deformation due to compaction pressure cause a bond area between particles during the powder compaction process (Sun, 2011). The amount of bond area between the particles remains constant after there is no compaction process and ejection of the tablet from a die that can produce a tablet intact.

Conclusion

The fluconazole-tartaric acid (FLU-TAR) co-crystal has been successfully prepared using the USSC method and ethanol as solvent. FLU-TAR co-crystal has a distinctive crystal morphology, powder X-ray diffraction pattern, and DSC thermogram. Moreover, the FLU-TAR co-crystal has better mechanical properties than pure fluconazole. Therefore, co-crystal can be used as a raw material in pharmaceutical tablet preparation with a direct compression method.

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