Enhancing the Solubility of Ketoconazole via Pharmaceutical Cocrystal

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Abstract. This present research is to synthesized and characterized cocrystal of ketoconazole through cocrystallization process in order to improve solubility properties of ketoconazole. Ketoconazole cocrystal synthesized by the slurry method and characterized using diffractometry (Powder X-Ray Diffraction), Thermogram (Differential Scanning Calorimetry), Microscopy (Polarizing microscope), FTIR spectroscopy and solubility analysis were performed to evaluate the cocrystal. The PXRD diffractogram of cocrystal ketoconazole is different compared to pure component. New peaks characteristic of cocrystal appear at a 2θ value of 16.94° and 24.58°. In addition, synthesized cocrystal have unique habit crystal, melting point and FTIR spectrum compared to single component. The ketoconazole cocrystal from slurry method showed an improved solubility by 50 times compared to ketoconazole. This study showed that cocrystallization between ketoconazole and ascorbic acid were successfully formed and enhanced the solubility of the drug.

1. Introduction
Crystal form is a solid phase that commonly exists in active pharmaceutical ingredient (APIs) and more stable than the amorphous drugs. However, about 80% of the crystalline form of APIs that in the market has solubility problems. Absorption an oral route of the pharmaceutical dosage form with low solubility and high permeability is restricted due to their solubility problem. Therefore, improvement of the physicochemical properties crystal form of APIs such as solubility is one of the most interest issues in drug development [1].

Recently, modification of various solid state such as polymorphs, salts, solvates, hydrates has been reported to improve the physicochemical properties of APIs. Cocrystal is emerging as an essential alternative to polymorph and salts during the solid phase selection APIs. Pharmaceutical cocrystal defined as solid which are a crystalline material composed of two or more molecules in the same crystal lattice [2]. During the past years, many cocrystals have been designed to improve physicochemical properties of APIs such as solubility/dissolution [3], hygroscopicity [4], chemical stability [5], mechanical properties [6], and bioavailability [4].

Ketoconazole is a broad-spectrum imidazole antifungal agent and administered by topical and oral. Being a BCS class II drug [7], the chemical structure of ketoconazole has a visible hydrophobic site and weak basicity that promotes to its poor aqueous solubility [8]. Solid dispersion formulation with beta-
cyclohexane and hydroxypropyl beta-cyclodextrin have been used to increase solubility and dissolution rate of ketoconazole [9].

In this investigation cocrystal formation of ketoconazole with acceptable pharmaceutical coformer, ascorbic acid was evaluated. The synthesized cocrystal was characterized using various analytical instrumentation and methods. The influence of coformer solubility on cocrystal was investigated further.

2. Experimental details
Ketoconazole was purchased from PT. Dexa Farma. The cocrystal ketoconazole was synthesized using slurry methods. Equimolar (1:1 mol ratio) quantities of ketoconazole and ascorbic acid were dissolved in ethanol-water solution (7:3 v/v). Each mixture suspension then stirred in the beaker glass with a magnetic stirrer for 30 minutes and then the slurries were filtered and stored for 24 hours in a desiccator. Different methods have been applying for the characterization of solid cocrystals, such as diffractometry (Powder X-Ray Diffraction), Thermogram (Differential Scanning Calorimetry), Microscopy (Polarizing microscope), FTIR spectroscopy.

2.1. Solid State Characterization by PLM
About 1-2 mg of ketoconazole, ascorbic acid and cocrystal placed on object glass. Adjust the lighting on the microscope so that the habit of the crystals can be observed well. Setting the objective lens on the enlargement of 40, 200, and 400x, the sample observed through the application AnalySIS getIT 5.1 version in the host computer which is connected with the camera on the ocular lens CMOS microscope.

2.2. Solid State Characterization by DSC
About 10-20 mg powder samples placed on the alumina crucible at DSC instrument. Thermal analysis was carried out in a temperature range of 30-250 °C with a heating rate of 10 °C per minute and with a flow of nitrogen gas.

2.3. Solid State Characterization by PXRD
A total of 100-200 mg samples on the sample holder are placed on X-ray diffractometer stage. Analysis was carried out in the range of diffraction angle 2θ 5 - 45 ° with step size 0.002° using using CuKα radiation (Kα1 = 1,54060 nm; Kα2 = 1,54439 nm) at 40kV and 35mA.

2.4. Solid State Characterization by FTIR
About 10 mg of sample was mixed with 200 mg of KBr crystals, then KBr pellets were made. Measurements using an infrared spectrophotometer (JASCO, MD, USA) and carried out with a wave number range 4000-400 cm⁻¹

2.5. Solubility measurement
Weighed about 50 mg of sample and put into a vial containing 20 ml of aqua DM, then dissolved with the aid of a magnetic stirrer at room temperature for 24 hours or until the solution saturated. The Suspension was filtered and its absorption is measured at the maximum wavelength using a UV-Vis spectrophotometer

3. Results and discussion
From polarized light microscope in Figure 1, several morphologies were identified in the sample. Cocrystal has a different crystal habit compared to its starting components. The crystal habit of APIs is one crucial variable in pharmaceutical manufacturing that can influence its mechanical properties and it affects the performance of final dosage form [10]. The melting point is a physical property which can be determined by the temperature at which the solid phase at equilibrium with the liquid phase. The DSC trace of ketoconazole, ascorbic acid, and cocrystal are shown in figure 2. The melting points of cocrystal (164.8 °C) are different from those of ketoconazole (148.1°C) and ascorbic acid (196.4°C). DSC analysis of cocrystal shown endothermic peak which between a melting point of the single
compound. This result was in agreement with previous reports that melting points of 50 reported cocrystal samples and found that 51% of cocrystal had melting points between those of the API and coformer [11]. The changes in melting points may be attributed to change in powder geometry of samples during preparation [12].

Since every solid phase produces its characteristic powder pattern owing to the unique internal crystal structure, PXRD is a fundamental tool for the identification of a new crystalline phase. Figure 3 showed the PXRD of ketoconazole cocrystal compared to ketoconazole and ascorbic acid. The diffraction pattern of ketoconazole cocrystal was noticeable from the individual compound. Ketoconazole cocrystal exhibited characteristic crystalline peaks at a 2θ value of 16.94° and 24.58° which not found in the PXRD pattern of a single compound. This unique peak in the diffractogram could suggest the existence of an interaction between ketoconazole and ascorbic acid to form a new crystalline phase (cocrystal).

FTIR spectroscopy can be used to identify the formation of the new crystalline phase. The changes in hydrogen bonding due to change formation solid phase can be directly correlated with the change in vibrational frequencies of the functional group [13]. The FTIR spectrum of ketoconazole shows the presence of unique peaks at 1647 cm\(^{-1}\) (C=O stretch), 1582 cm\(^{-1}\) (C=C aromatic symmetric stretch), and 1512 cm\(^{-1}\) (C=C aromatic asymmetric stretch. From the FTIR spectrum (Fig. 4) reveal the changes in the IR bands of the cocrystal compared to the parent compound. The main IR spectrum peaks of C=O (stretch) groups of ketoconazole, ascorbic acid are observed at 1647 cm\(^{-1}\) and 1755 cm\(^{-1}\). The cocrystal shows IR peaks at 1643 cm\(^{-1}\); and this shifted peak indicates the presence of hydrogen bond formation between ketoconazole and ascorbic acid. The solubility of ketoconazole and cocrystal was determined at 24 h in distilled water. The results of solubility analysis show that solubility value of ketoconazole and cocrystal were 10 µg/ml and 500 µg/ml respectively. The present of soluble coformer (ascorbic acid) in the internal crystal structure of cocrystal increased the solubility of ketoconazole.

![Image](image_url)

**Figure 1:** PLM image of (a) Ketoconazole, (b) ascorbic acid, (c) cocrystal

4. Conclusion

This study presents synthesized, characterization and solubility of ketoconazole and ascorbic acid cocrystal using the slurry method. New crystalline phase (cocrystal) was confirmed from the polarized microscope, PXRD, DSC and FTIR. Solubility nature of the cocrystal with high solubility coformer can be applied as a tool to improve physicochemical solid form. The improved solubility of ketoconazole cocrystal may potentially enhance the dissolution and absorption profile.
Figure 3: DSC thermograms of (a) ketoconazole, (b) ascorbic acid, (c) cocrystal

Figure 3: X-Ray Diffraction pattern of (a) ketoconazole, (b) ascorbic acid, (c) cocrystal

Figure 4: FTIR spectrum of (a) ketoconazole, (b) ascorbic acid, (c) cocrystal
5. Reference

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