

Physicochemical and Micromeritics Properties of Ketoprofen- Tartaric Acid Binary System

by Achmad Himawan

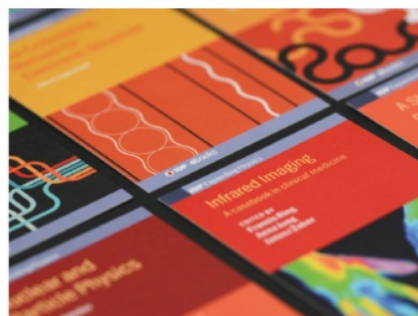
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Physicochemical and Micromeritics Properties of Ketoprofen-Tartaric Acid Binary System

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Abstract. Physical characteristics of pharmaceutical active ingredients can be modified by molecular structure rearrangement inside its crystal lattice. Cocrystallization involved the formation of new crystal structure from two different crystal components. In its application in the pharmaceutical field, the formation of cocrystals can comprise the interaction between an active ingredient and an inert substance or between two different drugs. This study aimed to synthesize cocrystal from Ketoprofen and Tartaric Acid. Ketoprofen and Tartaric acid were ground with mortar for 10 minutes prior dissolving in methanol at 40°C with continuous stirring. The solution then filtered and evaporated at ambient temperature. The resulting crystal was ground before further characterization. The individual component and cocrystal were characterized using FTIR, Differential Scanning Calorimeter (DSC) and Powder X-Ray Diffractometer (PXRD). The results show that the acquired crystal mass, KET-TAR, is a mixture of a semi-crystalline phase and its non-interacting precursors. New phase formation has been confirmed from both PXRD and DSC data. KET-TAR shows greater micromeritics properties compared to Ketoprofen with the value of angle of repose of, bulkiness, Carr's Index, Hausner's Ratio and Porosity are 25.3°, 1.8, 16.667, 1.200 and 61.7% consecutively. Overall improvement in micromeritic properties are clearly shown in the results.

1. Introduction

One of the biggest challenges in the field of pharmaceutical industry is to find a way to improve physicochemical characterization of active pharmaceutical ingredients (API)/drug molecules. Solubility, dissolution rate, melting point, tendency to absorb moisture and compressibility of the API and/or excipients can affect the bioavailability, design, processing, production, and stability of the final products [1]. Cocrystallization is a promising approach to solve this problem due to its ability to improve the physicochemical properties of APIs [2].

Ketoprofen ((RS)-2-(3-benzoylphenyl)propanoic acid) is a propionic acid derivative which belongs to NSAID class and works by inhibiting the prostaglandin synthesis. Ketoprofen is widely used in the formulation of OTC and/or ethical drug formulation in the form of coated tablets, capsule, soft capsule, topical formulation (gel), liquid spray, patch, and suppositories. Due to its low water solubility, it has some limitation in topical and parenteral formulations [3]. Ketoprofen is a light and bulky materials that may cause problem during manufacturing process especially in solid pharmaceutical production.

A pharmaceutical cocrystal can be designed by crystal engineering to improve the solid state properties of drug substance without altering its intrinsic structure [4]. Cocrystallization process is a

form of supramolecular self-assembling that can be used to improve the properties of APIs such as dissolution rate, mechanical properties, and stability [5]. Generally, by using water-soluble cofomers, cocrystal with better water solubility will be acquired. [6].

In the cocrystallization process, a partner molecule is chosen from a wide range of molecules that can form hydrogen bonds, so it will be able to produce a stable supramolecular synthon with the drug precursors. For pharmaceutical purposes, both the active ingredient and cofomer should be a safe and non-toxic material when consumed by humans. Most of organic acids or molecules with amino groups is selected because it is able to form a stable cocrystal [7].

This research is focused on the modification of ketoprofen crystal through cocrystallization using tartaric acid which is an organic acid based cofomer to acquire cocrystal with superior physicochemical characteristics and micromeritic properties.

2. Research Methodology

2.1. Materials and Instrumentation

Ketoprofen was purchased from CV Pharnalab and used without further purification. Any other ingredients used were analytical grade. L(+)-Tartaric acid was used in this research. The list of instrumentation used in this research is Spectrophotometer FTIR (Shimadzu), Powder X-Ray Diffractometer (MaximaX), Differential Scanning Calorimeter (TA Instruments).

2.2. Sample Preparation

Equimolar mixtures of Ketoprofen (KT) and Tartaric Acid (TA) was prepared by using solvent evaporation method. A quantity of KT and TA (equal to 0,1 molar each) was weighed and ground with mortar for 10 minutes. The powdered mass then transferred to a beaker glass and dissolved in warm methanol (40°C) with constant stirring. The stirring was continued until a clear solution is obtained. The solution then filtered through a filter paper into a crystallization dish and the solvent was evaporated at room temperature until a dry mass is obtained. The mass than pulverized and stored in airtight container.

2.3. Sample Characterization

2.3.1. *FTIR Spectroscopy.* The infrared spectrum of precursors and product was examined using FTIR Spectrophotometer. Samples were prepared using KBr and scanned from 400 to 4000 cm^{-1} . The IR spectrum was obtained by plotting %transmittance against wavelength number [1].

2.3.2. *Thermal Analysis.* The thermal profile of KT, TA, and KTTA was obtained using differential scanning calorimetry method as described in the literature with modification. The sample was scanned using DSC instrument from 30°C to 250°C in aluminium crucible under Argon atmosphere. The scanning speed was 3°C/minute [2,8]

2.3.3. *PXRD Analysis.* Powder X-Ray diffraction pattern from KT, AT, and KTTA has obtained using PXRD instrument. The sample was scanned using X-Ray with Cu K2 α lamp as the source. The sample was tested at 40 kV voltage and 30 mA currents. The diffractogram was obtained at the flat plan at $\theta/2\theta$ with 2θ value ranged from 5-50° and scanning speed 2°/minute [3,9]

2.3.4. *Micromeritics Properties.* Bulk density, tapped density, true density, flow speed and angle of repose of the samples were determined using standard method and from that data, the Hausner Ratio, Carr Index, Porosity and Bulkiness of the sample was determined [10].

3. Result and Discussion

In this research, the KTTA cocrystal was synthesized using solvent evaporation method. Methanol was chosen as the solvent because theoretically, ketoprofen and tartaric acid have a similar solubility in methanol. Solvent selection in cocrystallization is a critical process since it determines the output of the process. Selecting a solvent in which the individual component have similar solubility but the cocrystal product has a lower solubility is one of the methods that can be used [7]. Solvent evaporation works by forming a thermodynamically stable cocrystal when the complementary molecules have higher tendency to form hydrogen bonding with the drug rather than theirs [11].

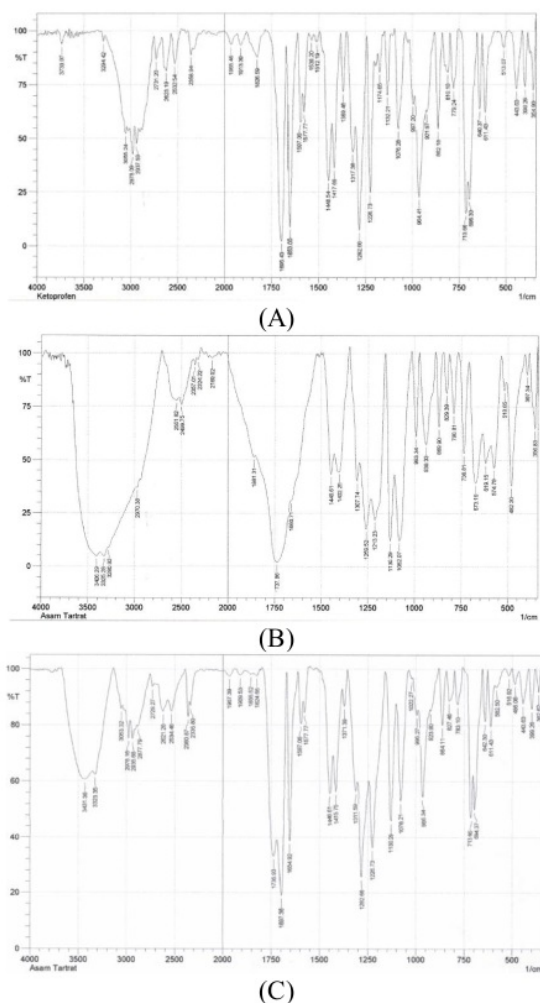


Figure 1. FTIR spectrum of Ketoprofen (A), L(+)-Tartaric Acid (B) and KTTA (C)

Other research had predicted the formation of cocrystal using virtual screening method. In that research, Ketoprofen and Citric Acid were predicted to be able to form cocrystal through the formation of hydrogen bonding [12]. A similar mechanism is predicted to happen when tartaric acid is used as

the cofomer. Other research claims to successfully synthesize ketoprofen cocrystal using malonic acid as the cofomer [13].

KTTA, KT, and TA were analyzed using FTIR spectrophotometer and the IR spectrum of these samples was shown in Figure 1. Ketoprofen spectrum was characterized by absorption peaks at 3055.24, 1695.43 and 1653.00 which correspond to aromatic C-H stretching, acid C=O stretching, ketone C=O stretching, and also at 1597.06 and 1448.54 which correspond to aromatic C=C stretching respectively [14]. Tartaric acid IR spectrum was characterized by absorption peak at 3325.28 which correspond to -OH stretching and 1735.11 which correspond to C=O stretching [11]. KTTA infrared spectrum shows both KT and TA absorption peak. KT absorption peak at 1448.54 shifted to 1446.61 and absorption peaks of TA are shifted from 1737.86 and 3325.28 to 1735.93 and 3323.35.

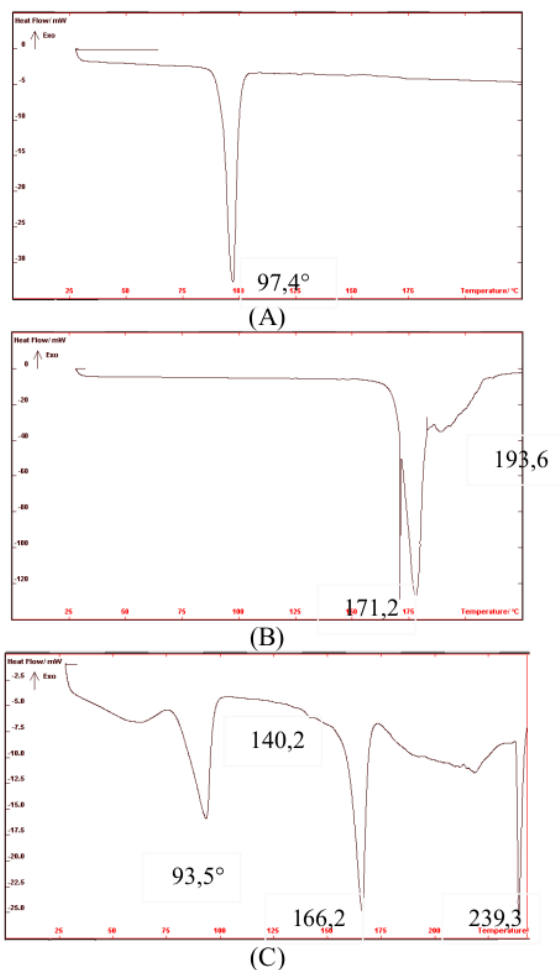


Figure 2. Thermogram of Ketoprofen (A), L(+)-Tartaric Acid (B), dan KTTA (C)

Thermal analysis with DSC is performed to find out the change in thermodynamic properties of solid materials [15]. KT, TA and KTTA thermogram is shown in figure 2. The results show that the KTTA thermal property is different from the precursors. An endothermic reaction at 97,4°C was

observed in KT and in TA endothermic melting reaction and endothermic phase change reaction was observed at 175.8°C and 193.6°C. In KTTA, at least four thermal events are observed and one of them corresponds to glass transition reaction.

The endothermic melting reaction is observed at 93.5°, endothermic reaction observed at 166.2°C correspond to phase transition reaction and the endothermic forming reaction is marked by the temperature at 239.3°C. A glass transition event is observed at 140.2°C which is not observed in both KT and TA. Transition glass temperature is a unique property of solid amorphous and semi-crystalline substance. The presence of a glass transition temperature indicates the presence of a semi-crystalline phase in KTTA [15].

The change in molecular structure in the crystal lattice can be examined using PXRD. The comparison between KT, TA and KTTA diffractograms are shown in Figure 3. The three highest peaks in KT are recorded at 44.05°, 37.83°, and 18.29° and for TA are recorded at 44.06°, 37.82° and 31.53°. In KTTA, the three highest peaks are observed at 22.64°, 18.25°, and 20.44°. This diffraction pattern indicates the formation of new crystalline phase [16]. Diffractograms from the KTTA differs with its precursors but the peak from both the KT and TA are still noticed in the product diffractograms. It is possible that in this product, un-interacted precursors molecules still present and interfere with the results [3]. If the results also compared with the DSC results, the diffraction pattern observed in the KTTA may be correlated to a semi-crystalline phase.

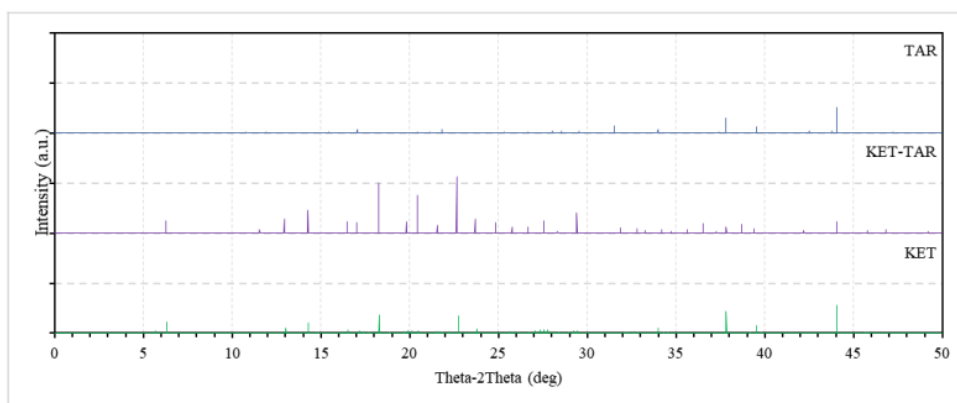


Figure 3. X-Ray Diffractogram comparison of TA (top), KTTA (middle) and KT (bottom)

In a solid dosage form formulation, the flow powder properties like the angle of repose and compressibility need to be considered since it affects the quality of the final preparation. In this research, the powder characteristics such as density, porosity, bulkiness, flow speed, the angle of repose, Carr's Index and Hausner's Ratio is determined for both KT and KTTA. The results reveal that KTTA has superior properties compared to Ketoprofen ($\theta = 46-55^\circ$, $CI > 38$, $HR > 1.6$). According to the angle of repose, KTTA ($\theta = 25-30^\circ$) has an excellent flow property and from its Carr's Index and Hausner Ratio, KTTA ($CI = 26-20$, $HR = 1.19-1.25$) has a good flow property.

The cocrystallization process also could reduce the bulkiness of KT. From the density determination, KT is a very bulky and light powder which often resulted in the handling difficulty. The powder properties improvement in KTTA may contribute to a better powder flow into the dies [10]. The complete experimentation results of powder properties are shown in Table 1 and Table 2.

Table 1. Powder Flow Properties

No.	Sample	Flow Properties		Remark
		Angle of Repose (°)	Flow Speed (g/s)	
1	Ketoprofen (KT)	47.9	0.1	Poor
2	KTTA	25.3	2.5	Excellent

Table 2. Density and Porosity

No.	Sample	Density			Carr's Index	Hausner's Ratio	Bulkiness	Porosity (%)
		Bulk	Tapped	True				
1	Ketoprofen	0.294	0.476	1.429	38.235	1.619	3.4	79.4
3	KTTA	0.556	0.677	1.450	16.667	1.200	1.8	61.7

4. Result and Discussion

The cocrystallization product, KTTA, consists of a mixture of semi-crystalline phase with possible unreacted precursors. The product shows superior flow properties and bulkiness compared to Ketoprofen.

5. Acknowledgement

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