Study on The Cocrystal Formation of Ibuprofen and Oxalic Acid via Evaporation Method

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Abstract*— Co-crystallization is the process where the combination of two compound which are active pharmaceutical ingredient (API) compound with the co-former by the non-covalent interaction. This process is believed that it can enhanced the physicochemical properties of the API including solubility, stability, dissolution rate, melting point and its bioavailability. Due to this, the research for the co-crystallization of the Ibuprofen and oxalic acid as it co-former had conducted by using the slow evaporation method. The analyzation and characterization of this co-crystal had conducted by using the optical microscope, Fourier transform infrared spectroscopy (FT-IR), differential scanning calorimeter (DSC) and X-ray diffraction (XRD). The observation using optical microscope had shown that the cocrystal grew in the dendrite and rod shape. From the characterization of the cocrystals in FTIR, it shows the shift of peak which can be shown the cocrystal structure had performed. Then, the DSC showed that the melting point of cocrystals were higher than the pure ibuprofen. This showed that the cocrystal had higher thermodynamic stability than the pure its API. The characterization of the IBP:OA cocrystal by using the XRD had proved that there are new crystallographic structure formed by comparing it with the pure compound. These results showed the cocrystals had formed.

Keywords*— Co-crystallization, ibuprofen, oxalic acid, solubility, stability.

I. INTRODUCTION

Active pharmaceutical ingredient (API) is a substance that is active containing in the pharmaceutical products such as tablets. The dosage of the API is according to their functioning as the treatment or else give an effect to the diseases. This API usually mixed with the excipients to form the pharmaceutical medicine as it cannot be present in its own. However, this form poses the low solubility and stability. Therefore, the API is believed that it can enhanced their characteristic by forming the co-crystal which it combines with the co-former. The co-former selection is the challenging parts in forming a cocrystal. Its need a trial and error until the cocrystal is formed. The organic acid is likely to be used as coformer in cocrystallization process. For example, oxalic acid. Oxalic acid, $C_2H_2O_4$ is an organic compound which consists of two carboxylic acid. It is a strongest acid and acts as a reducing agent. It is also called as ethanedioic acid which usually presents in plants and vegetables. Its molecular weight is 90.03 g/mol.

The ibuprofen is a well knowns drug in nonsteroidal anti-flammatory drug(NSAID) for relieves pain named chemically as 2-(4-isobutylphenyl)propanoic acid. (al, 1984) It also used to relief the arthiritis, fever and act as analgesic. The physicochemical properties of the co-crystal such as solubility, bioavailability, stability, melting point and intrinsic dissolution are an important in the development of the APIs. The characteristics of ibuprofen are it has unique physicochemical properties as its pKa value is 4.4-5.2, it also an amphiphilic that leads it to unique interaction with the lipid membrane and it has a detergent-like characteristic. By obtaining those characteristics, it gives many advantages to the ibuprofen as an active pharmaceutical ingredient (API). (Rainsford, 2013) This ibuprofen, class II of the Biopharmaceutical Classification System has high permeability and low solubility in water. (Frederico L., 2013) Before this the ibuprofen had been supplying in a form of tablets. Therefore, the formation of the co-crystal of the ibuprofen and the oxalic acid is believed to enhance it solubility, stability and the dissolution rate. Based on the journal by Walsh et al 2003, the co-crystal of the ibuprofen with other API which is nicotinamide had been discovered to enhance its solubility by the solvent evaporation method.

Solvent evaporation method

Solvent evaporation is one of the method used in producing co-crystal. It is a type of solvent-based crystallization technique. This technique is used the solvent to dissolve the mixture of API with conformer and then need to be evaporated until the co-crystal formed. This research has used the ethanol and propanol as its solvent. From Table 2.1, this method had been used in formation of paracetamol:4,4-dipyridil and piroxicam:saccharin co-crystals. In the pharmaceutical co-crystals, the compound that has the lower solubility, then the other one will be precipitate out when there is difference in their solubility.

Due to this condition, the polymorphism and the intermolecular interaction are also necessary to make the success of the co-crystal formation. This method requires higher volume of the solvent. (Tanvee Patole, 2014)

Analytical method to analyze the co-crystal

Analytical method is used in this research to analyze or characterize the co-crystal formed. The analytical method of this research is analyzing the co-crystal with the optical microscopy, X-ray Powder Diffraction (XPRD), Diffraction Scanning Calorimetry (DSC) and Fourier Transform Infra-Red Spectroscopy (FTIR).

The optical microscopy is a technique that used the optical microscope to determine the morphology of the co-crystal. Optical microscope has a magnification system that visualized the structure of the compound which is co-crystal more clearly to the naked eye by an objectives lens through the eyepiece. The morphology of the co-crystal or crystal can be related to its size, shape of faces and the angular relationships. The form of the ibuprofen-oxalic acid co-crystal is determined by using this technique. Then being comparing with the pure compound form. The ibuprofen has form like plate shape.

X-ray Diffraction method used to obtain the unit cell dimension which is co-crystal information by analyzing its phase identification. This phase identification of the co-crystal is obtained by directing the monochromatic radiation produced from the filtration of the cathode ray tube to the co-crystal sample. The co-crystal sample must be finely grounded to produce powder form of co-crystal. This analyzation occurs in term of the d-spacing and also must obey the Bragg's law which is $n\lambda=2d \sin \theta$ that relates the wavelength of the electromagnetic radiation to the diffraction angle 2θ. (Deshpande, 2014) Figure 1.10 shows the relative intensity of the ibuprofen, nicotinamide, co-crystal and ibuprofen:nicotinamide 1:1 (wt:wt) against $2^{o}\theta$. From the graph, the most significant peaks are at the 9.50 and $12.662^{o}\theta$ that indicates the new crystallographic structure. This study also proved to be consistent with the literature data. (Frederico Luis Felipe Soares, 2013)

Diffraction Scanning Calorimetry is the method used to identify the melting point of the co-crystal. The melting point of the co-crystal is an important value to determine the purity of the co-crystal or the API elsewhere. The melting point of the pure solids usually very narrow in value such as $1\text{-}2^{o}C$ and will be lower as there is an existence of the impurity in the compound. Figure 1.11 shows the peaks which indicate as the melting points of Carbamazepine (CBZ), cinnamic acid (CIN) and CBZ-CIN co-crystal. It proved that the melting point of co-crystal which is $144^{o}C$ located in between the melting points of carbamazepine and cinnamic which are $190^{o}C$ and $133^{o}C$ respectively.

Lastly, the method that usually used to identify the type of the co-crystal formed is Fourier Transform Infra-Red Spectroscopy (FTIR). The chemical functional groups of the samples which are co-crystal and its composition are determined by using this equipment. Every type of bond gives different natural frequency of vibration. Therefore, different absorption pattern produced for the different structure of molecules. (Farhana Akter, 2015) Figure 1.12 shows the FT-IR spectra of the ketoconazole-benzoic acid co-crystal. The main peak of the C=O bond (stretch) in the ketoconazole (KTZ) and benzoic acid (PABA) was observed at the and 1666 cm^{-1} respectively. While the peak of the co-

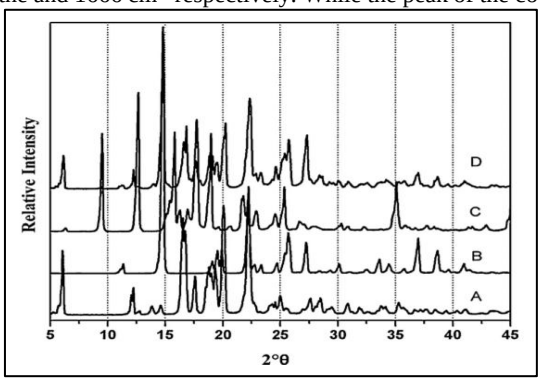


Figure 1.10: Diffractogram of: (A) ibuprofen, (B) nicotinamide, (C) co-crystal and (D) ibuprofen:nicotinamide 1:1 (wt:wt). (Frederico Luis Felipe Soares, 2013)

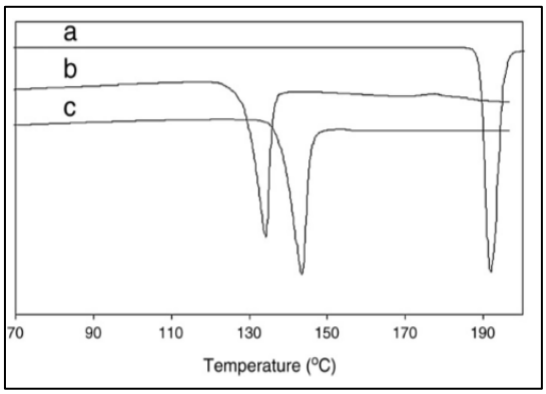


Figure 1.11: DSC thermograms of (a) CBZ, (b) CIN (c) CBZ–CIN. (Ali Shavanfar, 2013)

crystal can be seen at 1647 cm^{-1} which refer to the carbonyl group of the KTZ that cannot be relate to the hydrogen bond formation between KTZ-PABA co-crystal. But the second of co-crystal shows the carbonyl group that referred from the PABA structure to show that there was hydrogen bond form between the KTZ and the PABA. It proved that there were KTZ-PABA co-crystal form.

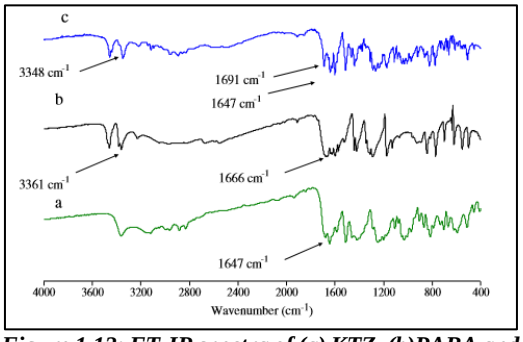


Figure 1.12: FT-IR spectra of (a) KTZ, (b)PABA and (c) KTZ–PABA. The arrows shown indicated the significant changes in vibrational bands in IR spectra. (Ali Shayanfar, 2014)

I. METHODOLOGY

A. *Materials*

Oxalic acid, ibuprofen, ethanol, 1-propanol, vials, orbitary shaker, hot plate, electric balance.

B. *Preparation of ibuprofen-oxalic acid.*

There are 5 mole ratios of ibuprofen to the oxalic acid used in this research to form the co-crystal. It was started with 0.5:1 mole ratio where 2.292g of the ibuprofen mixed with 0.639g of oxalic acid. Then, the solvent which was 5ml of ethanol was added to dissolve the ibuprofen and oxalic acid. The solution then was heated at 50^{o}C and increased until all the solute dissolved. These steps were repeated for the 4 different mole ratio (1.5:1, 2.5:1, 3.5:1, 4.5:1) to find the most suitable mole ratio to produce co-crystal of ibuprofen and oxalic acid. The concentrations for each mole ratio were tabulated in the Table 3.2.1. For the next experiment, the ibuprofen and oxalic acid were dissolved in the solvent ethanol. The concentrations for each molar is stated in Table 3.2.1.

Table 3.2.1: Mass of ibuprofen and oxalic acid for each molar ratio in ethanol solvent.

Molar ratio (IBP:OA)	**Mass of ibuprofen, IBP (g)**	**Mass of oxalic acid, OA (g)**
0.5:1	2.929	0.639
1.5:1	2.929	1.918
2.5:1	2.929	3.916
3.5:1	2.929	4.474
4.5:1	2.929	5.753

C. *Analyzing the co-crystal of ibuprofen-oxalic acid with optical microscopy*

The sample is taken from the solution. The morphology of the ibuprofen-oxalic acid co-crystal is observed by using optical microscope. The equipment used is the Meiji Techno 1599 optical microscope. It is completed with the Zabecco software to obtain the data.

D. *Analyzing the co-crystal of ibuprofen-oxalic acid with Fourier Transform Infra-Red Spectroscopy (FTIR)*

Fourier Transform Infra-Red spectroscopy used in this study is Thermo Nicolet to analyze the sample of ibuprofen-oxalic co-crystal. This equipment measures the IR spectra of the sample by using the wavenumbers in the range of 1500 to 4000cm^{-1}. This method is to study the molecular interaction of the ibuprofen-oxalic acid co-crystal.

E. *Analyzing the co-crystal of ibuprofen-oxalic acid with Differential Scanning Calorimetry*

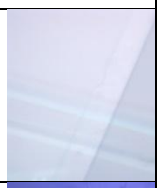
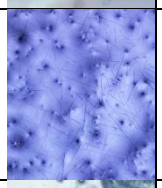
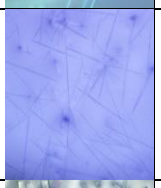
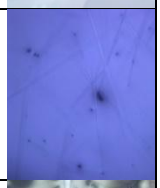
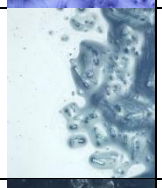
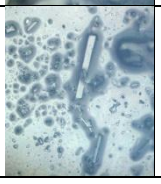
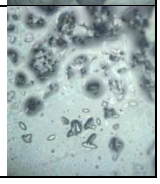
Then, the sample being weighed and analyzed using the DSC 820 (Metler Toledo) equipment. About 8 mg of the co-crystal formed is heated by using the heating rate of 10^{o}C per minute. The nitrogen gas is used with the temperature 0-400^{o}C. The results of the measurement will be recorded.

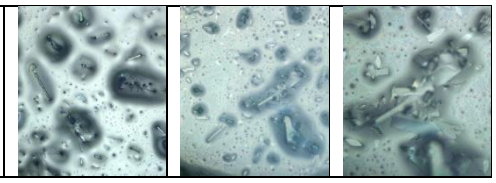
F. *Analyzing the co-crystal of ibuprofen-oxalic acid with the X-ray Powder Diffraction (XRPD)*

The sample is dried by using the oven at 40^{o}C and being crushed using portal and mortar to get the co-crystal in powder form. The sample of co-crystal formed is analyzed using the powder diffractometer (Rigaku) with Cu Kα, tube voltage of 40 kv, current of 40 Ma. Then, the sample is placed on a thin glass and the patterns are being examined from 3^{o} to 40^{o} at 2θ values with the steps size 0.01^{o} per minute.

II. RESULTS AND DISCUSSION

A. *Observation the co-crystal of ibuprofen-oxalic acid with optical microscopy*

Molar ratio (IBP:OA)	**4x magnification**	**10x magnification**	**20x magnification**
0.5:1			
1.5:1			
2.5:1			
3.5:1			

4.5:1	

For the ethanol solvents, the crystals grew like a thin rod shape in the molar ratio of 0.5:1 and started to formed dendrite shape in 1.5:1 ratio with more branches as shown in Table 1. The observation for the 2.5:1 and above, the observations were not so cleared as the crystal had broken during the preparation for the slide. There were less solutions left in the vials which most of its were converted into crystal form. That was because the structures of crystal were stick together among itself also it stacked to the inner wall of vials very well. The crystal form in the 2.5:1 seems like thin rod shape. The same shape has figure out from the 3.5:1. The 4.5:1 has shown the crystals like leave plate shape and the large crystal form is like rod shape. From these results, its proved that the cocrystal of ibuprofen and oxalic had formed due to change of the structure and shape from the pure component.

B. The analysis of co-crystal of ibuprofen-oxalic acid with Fourier Transform Infra-Red Spectroscopy (FTIR), differential scanning calorimeter (DSC) and X-ray diffraction (XRD).

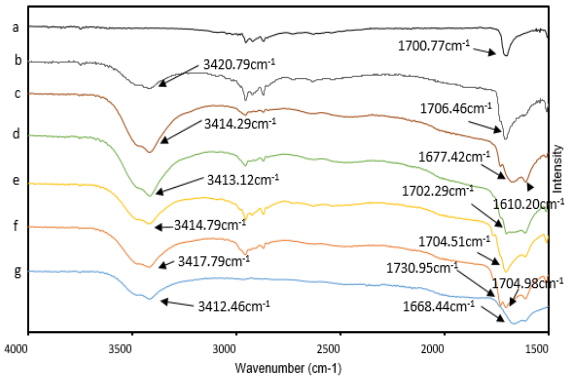


Figure 1: FT-IR results for the pure IB(a), cocrystal of 0.5:1(b), 1.5:1(c), 2.5:1(d), 3.5:1(e), and 4.5:1(f) molar ratio and pure oxalic acid(g).

Figure 1 shown above was the result from the FT-IR analyzation. The analyzation had been performed for the pure ibuprofen, pure oxalic acid and cocrystal in 0.5:1, 1.5:1, 2.5:1, 3.5:1, 4.5:1. The FT-IR spectrum for the ibuprofen gave peaks at 1506.96cm^{-1} which can assign as aromatic ring C=C-C, 1700.77cm^{-1} as carboxylic acid, 2867.90cm^{-1} and 2954.19cm^{-1} as methyl C-H. While for the oxalic acid, the peak had formed at 3412.46cm^{-1} and 1668.44cm^{-1} which it can present as the hydroxy group OH and C=C respectively. The shift of peaks can be seen in the cocrystal 0.5:1 molar ratio as the peaks that can assigned as carboxylic acid is at 1706.46cm^{-1}, 2.5:1 molar ratio at 1702.29cm^{-1}, 3.5:1 molar ratio at 1704.51cm^{-1}, and 1704.98cm^{-1}. The new peaks for the molar ratio 4.5:1 appears at 1730.95cm^{-1} which can be assigned as ester or aldehyde functional group. However, for the ratio 1.5:1 cocrystal, the peaks of oxalic acid at 1668.44cm^{-1} had shifted to 1677.42cm^{-1}. These peaks are assigned as the C=C. The new peak at 1610.20cm^{-1} presented in the molar ratio 1.5:1 which can be indicated as aromatic ring. Another peak had formed for the oxalic acid characterized as hydroxy group, OH which is at 3412.46cm^{-1}. This peak had shifted to 3420.79cm^{-1}, 3414.29cm^{-1}, 3413.12cm^{-1}, 3414.79cm^{-1}, 3417.79cm^{-1} at molar ratio 0.5:1, 1.5:1, 2.5:1, 3.5:1, 4.5:1 respectively. The Table 2, had listed the peaks of the cocrystal formed during FT-IR analyzation. Figure 2 represents the curves for the cocrystal of the 0.5, 1.5, 2.5, 3.5 and 4.5 oxalic acid, pure ibuprofen. The peaks of 0.5:1, 1.5:1, 2.5:1, 3.5:1 and 4.5:1 cocrystals show at temperature 101.04, 101.34, 101.04, 101.53 and 101.34^{o}C respectively. While the pure ibuprofen shows a melting point peak at 80.72^{o}C which are endothermic signal. These showing that the cocrystals have higher thermodynamic stability than the API which is ibuprofen itself. The higher energy was needed by the cocrystals to break the

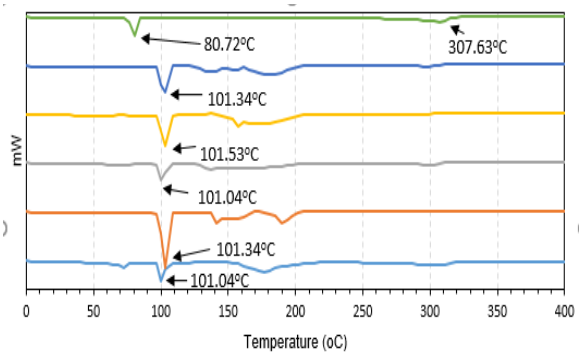


Figure 2: DSC curves of the pure IB(a), cocrystal of 0.5:1(b), 1.5:1(c), 2.5:1(d), 3.5:1(e), and 4.5:1(f) molar ratio.

crystal lattice. Some research had presents the value of peaks appear for the oxalic acid from the characterization of the DSC was at 195.38^{o}C which is higher than the cocrystal melting point. (Oana Onija, 2012) These can be proved that the cocrystal had formed in the molar ratio of 0.5:1, 1.5:1, 2.5:1, 3.5:1 and 4.5:1. However, there are also another small peak appear after that. The instability of the cocrystal structure had observed due to the formation of another peaks in the all those cocrystals. These peaks indicate that there are instability are form in the that temperature. For example, ibuprofen showing one more peak at temperature 307.6^{o}C, therefore, the crystallinity of the ibuprofen was broken in that temperature. The peaks can be summarized in the Table 3.

Table 3: The temperature of other peaks formed at each cocrystals and pure ibuprofen.

Molar ratio	Temperature (^{o}C)
0.5:1	71.64, 178.90, 304.66
1.5:1	135.09, 189.83
2.5:1	75.20, 136.28
3.5:1	156.93, 290.77
4.5:1	65.27, 182.45, 294.76
Ibuprofen	307.6

Table 2: peaks formed for each cocrystals and ibuprofen and oxalic acid

Type of Bond	Wavenumber (cm^{-1})	Pure Ibuprofen	Pure Oxalic acid	Ethanol (0.5:1)	Ethanol (1.5:1)	Ethanol (2.5:1)	Ethanol (3.5:1)	Ethanol (4.5:1)
Hydroxy group, H-bonded, OH strength	3570-3200		3412.46	3420.79	3414.29	3413.12	3414.79	3417.79
Methyl CH_3, C-H	2970-2950/2880-2860	2954.19 2867.90		2954.68	2955.03	2954.97 2869.23	2954.67 2869.11	2955.30 2869.35
Acid O-H	3400-2500			2922.30 2869.20 2631.58			2539.93	
Ester Aldehyde	1750-1725 1740-1725							1730.95
Carboxylic acid	1725-1700	1700.77		1706.46		1702.29	1704.51	1704.98
C=C	1680-1620		1668.44		1677.42			
Aromatic ring stretch	1615-1580				1610.20			1611.40
Aromatic nitro compound	1555-1485	1542.04		1508.24				
Aromatic ring, C=C-C	1510-1480	1506.96					1508.34	

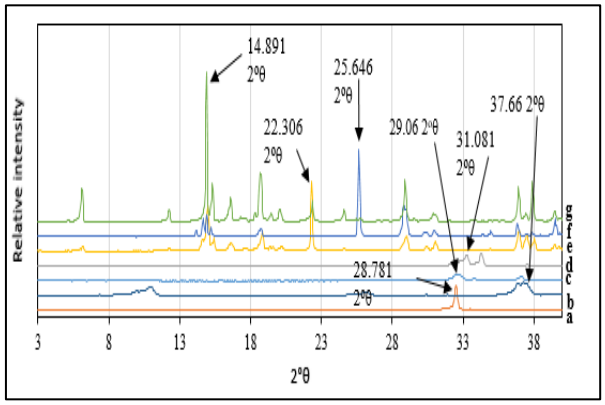


Figure 3: XRD results for the oxalic acid(a), IBP(b), cocrystal of 4.5:1(c), 3.5:1(d), 2.5:1(e), 1.5:1(f), and 0.5:1(g) molar ratio

While in Figure 3, it presents the diffractogram of the cocrystals and it pure compound which were ibuprofen and oxalic acid. The diffractogram of the ibuprofen can be observed the peaks at 2*θ*: 12.26, 24.54 and 37.66 2°*θ*. Then, the most significant peak of oxalic acid is at 30.98 2°θ. For the cocrystals, the significant peaks show at 29.06 2°θ for the 4.5:1 molar ratio, 29.0812°θ for the 3.5:1 molar ratio, 36.943, 22.306, 18.834 2°θ for the 2.5:1 molar ratio, 36.826, 28.847, 25.646, and 14.904 2°θ for 1.5:1 molar ratio and 37.406, 28.906, 18.671 and 14.89 2°θ for the 0.5 :1 molar ratio. These had been said that the new crystallographic structure had formed in the cocrystals.

III. Conclusion

The cocrystal of the ibuprofen and oxalic acid via evaporation method had formed the cocrystals. The observation of the cocrystal under the optical microscope gave the results of dendrite shape of the cocrystals. While the FT-IR result for cocrystal had shown the shift of peaks. The DSC results showed that the cocrystal had higher stability than the ibuprofen. The XRD diffractogram results presented that there was new crystallographic structure which proved that those were cocrystal formed. This proved that the cocrystal formation can improved the physicochemical properties of the API.

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