The Phase Transformation Assessment Of Ibuprofen-Citric Acid Cocrystal In Propanol And Ethanol Solution

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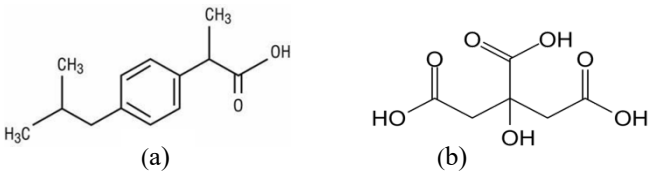
***Abstract*— The objectives of this research are to determine the phase transformation assessment of Ibuprofen-Citric Acid co-crystal in ethanol and propanol solution and to analyze the formation of ibuprofen-citric acid co-crystal using analytical equipment such as PXRD, DSC, FTIR and optical microscope. The stability and bioavailability of the Active Pharmaceutical Ingredients (API) are important for the product performance. However, a few drugs available in the market have low solubility and dissolution rate problem. Nowadays, pharmaceutical co-crystal has received great attention for the development of the drug as it can alter the physicochemical properties of API to increase the efficiency of a dosage form and the overall stability. Co-crystallization helps to increase the solubility of the active pharmaceutical ingredients. In this study, Ibuprofen will be selected as material of interest as it has low solubility. The method used in this study was slow-cooling method. In this study, the crystal formed has no pattern in term of ratio. The crystal formed showed plate-like shape whenever tested using the optical microscope. No new functional group formed in the crystals as compared to the pure components whenever analysed using the FTIR. The result of differential scanning calorimetry shows that all of the crystals formed are mixture instead of co-crystal. From this result, we can conclude that slow-cooling method is not suitable for co-crystallization of ibuprofen-citric acid.**

Keywords*— *Cocrystallization, Ibuprofen, Citric acid, Stoichiometric ratio, Slow-cooling

I. INTRODUCTION

Cocrystallization is an alternative method to mix two or more components within the same crystal lattice where the components interact via non-ionic interactions and are in neutral state (Rajesh Thipparaboina, 2016). The stability and bioavailability of the Active Pharmaceutical Ingredients (API) are important for the product performance. The dosing of consuming the drugs is the main concern. However, a few drugs available in the market face low solubility and dissolution rate problem. Low solubility of drug leads to the poor absorption and bioavailability, inadequate solubility for IV dosing, development challenges leading to raise the development cost and time thus burden the patients. In order to improve the pharmaceutical properties, the researchers regularly consider the alternative solid state forms to a free drug compound like polymorphs or salts. Unfortunately, some of the compounds do not have suitable site (basic or acidic) for proton transfer. Here where co-crystal can become practical alternative in drug formulation as co-crystals do not involve in proton transfer (Rosli, 2014). This method can help to increase the solubility of the active pharmaceutical ingredients (API). The intermolecular interaction occurred in co-crystal including hydrogen bonds, van der Waals, and π-π staking and the most agreeable geometry will point to a supramolecular network (Ushma Kotak, 2015). There are many methodologies for co-crystal screening is employed. As the examples is the solvent evaporation, slurry conversion and grinding technique (Ushma Kotak, 2015). In this study, co-crystallization is introduced to Ibuprofen to increase the solubility of Ibuprofen using slow-cooling method. Citric acid is used as the co-former and the ethanol and propanol solution as the solvent.



(a) (b)

Fig. 1 : Molecular Structure of (a) Ibuprofen (b) Citric Acid

Ibuprofen with molecular formula of $C_{13}H_{18}O_2$ is a non-steroidal anti-inflammatory drug largely used as antipyretic, analgesic and in the arthritis treatment. It has 206.29 g/mol molecular weight (Shui Wang, 2010). Recently, co-crystallization between Ibuprofen and nicotinamide has been done using analytical tools such as mid-infrared (ATR-FTIR), differential scanning calorimetry (DSC), X-ray diffraction (XRPD) and Raman spectroscopy. There are some studies shown that the bioavailability and mechanic stability of Ibuprofen has changed because of the interaction between nicotinamide molecules in the crystallographic motif of Ibuprofen. Solubility tests have indicated that the solubility of ibuprofen-nicotinamide co-crystal (IBP-NCT) is 7.5 times higher than the solubility of the pure ibuprofen crystal (Kelly, 2012). Hence, in this study, the formation of Ibuprofen-Citric Acid co-crystal in propanol and ethanol solution will be analysed using analytical equipment such XRD, DSC, ATR-FTIR and Optical Microscopy.

The choice of co-former will affect the solubility of the co-crystal. Co-crystal former should have at least one of the functional group selected from ether, aldehyde, ketone, alcohol or carboxylic acid (Jennifer McMahon, 2010). This is due to the hydrogen bonding rules which involve the arrangement of hydrogen bond donors and acceptors (Newman, 2009). Examples of the co-former that have been used are nicotinamide, oxalic acid, glutaric acid and terephthalaldehyde (Jayasankar, 2008). For this study, citric acid which has carboxylic acid functional group is selected as the co-former of this crystallization method as citric acid is highly water soluble, deliquescent co-former and is known to decrease water activity at high concentration (Jayasankar, 2008). Thus, this characterisation of citric acid can assist to increase the solubility of ibuprofen-citric acid co-crystal in Ethanol and Propanol solution. Moreover, citric acid contains hydrogen bond donor and acceptor groups which can be used in co-crystal design (Renu Chadha, 2012).

From previous study, ibuprofen is crystallized from methanol, ethanol, isopropanol, and hexane at 0.225 °C/min cooling rate. Ibuprofen crystals grow at all of the solution (H. A. Garekani, 2001). According to US Patent 4,476,248, Ibuprofen is heated to

temperature in the range 20°C to 60°C in methanol, ethanol, n-propanol and isopropanol. Then, the mixture is cooled to temperature 0°C to -20°C for about 0.5 to 3 hours to effect crystallization and precipitation of ibuprofen from the solution (Roger E. Gordon & Sanjay I.Amin, 1984).

The objectives of this research are to determine the phase transformation of Ibuprofen-citric acid co-crystal in propanol and ethanol solution and to analyze the formation of Ibuprofen-citric acid co-crystal using analytical equipment such as PXRD, DSC, ATR-FTIR and microscopy. Co-crystal can be the best option as it does not involves in proton transfer as some of the compounds do not have suitable site (basic or acidic) for proton transfer. Hence, it can be expected that the discoveries of this project will contribute to the potential use of drug-drug co-crystals in industrial drug formulation as it can give direct profits to the pharmaceutical field besides broader long term benefits to public health.

II. METHODOLOGY

A. Materials

Ibuprofen ($C_{13}H_{18}O_2$, MW of 206.29 g/mol (99% purity)) was obtained from SAFC, Citric Acid ($C_6H_8O_7$, MW of 192.12 g/mol (99.95% purity)) was obtained from SIGMA-ALDRICH, Ethanol (C_2H_6O, MW of 46.069 g/mol, (99.95% purity)) was obtained from EMSURE® and Propanol Solution ($C_3H_8O_2$, MW of 60.096 g/mol, (99.95% purity) was obtained from R&M Chemicals

B. Synthesis of Co-Crystal

Slow-Cooling Method

Eighteen samples of Ibuprofen and citric acid are prepared in the 5 ml of ethanol or propanol solution in the 20 ml of vial. The amount is calculated based on the molar ratio of ibuprofen to citric acid whereby the mole of ibuprofen is constant at 1 while the mole ratio of citric acid is varies from 0.5 to 4.5 using 0.5 as step size. The mixtures are heated at temperature 60°C until all of the solute dissolve. Once all of the mixtures are dissolved, the solution is left in the rotary shaker at 50 rpm for 17 hours to be cooled to temperature 20°C using cooling rate of 0.52°C per min (Brian C. Manor, 2016).

C. Characterization of Prepared Co-Crystal

The samples of the co-crystal are characterized using the optical microscope, ATR-FTIR, DSC and XRD using the following procedures.

a. Optical Microscope

The surface characteristics of ibuprofen citric acid co-crystals are observed using the optical microscope. The shape is determined and compared with the pure ibuprofen and pure citric acid.

b. ATR-FTIR

ATR-FTIR is used to identify the type of functional group in the samples. The spectrums of the samples prepared were recorded in the wavelength region of 4000 – 1500 cm^{-1}. Before placed the samples, the plate of FTIR Spectroscopy is wiped with acetone to remove any impurities.

c. DSC

In order to characterize the samples, about 7 mg samples are heated at the rate of 10°C/min using nitrogen gas. Firstly, the dried samples are weighted and placed in the aluminum cubicle.

d. XRD

The dry samples are be characterized with copper X-ray tube which operated at 40 mA and 40 kV between 3° to 40° for 2 θ (angle). The step size and step time were 0.01 and 1 second / step respectively. Before that, in order to obtain a fine crystal powder, the samples used for measurement was ground using a mortar and pestle.

III. RESULTS AND DISCUSSION

A. The Crystal Preparation

Table 1 Results of Ibuprofen-Citric Acid Co-Crystals Formed at Various Stoichiometric Ratio

Type of Solvent	Stoichiometric Ratio	Mass of Ibuprofen (g)	Mass of Citric Acid (g)	Crystal Form
Ethanol	1 : 0.5	2.93	1.36	No
	1 : 1	2.93	2.73	Yes
	1 : 1.5	2.93	4.09	Yes
	1 : 2	2.93	5.46	Yes
	1 : 2.5	2.93	6.82	Yes
	1 : 3	2.93	8.18	Yes
	1 : 3.5	2.93	9.55	Yes
	1 : 4	2.93	10.91	No
	1 : 4.5	2.93	12.28	Yes
Propanol	1 : 0.5	2.28	1.06	No
	1 : 1	2.28	2.12	No
	1 : 1.5	2.28	3.18	No
	1 : 2	2.28	4.24	Yes
	1 : 2.5	2.28	5.30	No
	1 : 3	2.28	6.36	Yes
	1 : 3.5	2.28	7.42	Yes
	1 : 4	2.28	8.48	Yes
	1 : 4.5	2.28	9.54	No

No Ibuprofen crystal was formed. The growth rate and the size of crystals are affected by cooling through its effect on supersaturation. At high degree of supersaturation (fast cooling), the crystal size generally decreases due to incomplete growth of a large number of small crystals. However, incomplete growth may also be the case at very low degree of supersaturation (slow cooling) due to the very long time required to complete growth (Nikolakakis, 2000).

In this study, the crystal formed has no pattern in term of ratio. The stoichiometry of a soluble co-former cannot be used as a straightforward criterion to estimate the co-crystal dissolution behavior, and consequently, increasing co-former stoichiometry in a co-crystal is not a reliable approach to optimizing drug solubility and dissolution (Matzger, 2016).

From Table 1, we can see that the crystal formed at all ratios except for 1 : 0.5 and 1 : 4 for ibuprofen-citric acid in ethanol. As in propanol, the crystal only formed at ratio 1 : 2, 1 : 3, 1 : 3.5 and 1 : 4. The crystals formed are analyzed using optical microscope, FTIR and DSC. PXRD test cannot be performed as the crystal formed too small in volume thus insufficient to be used for PXRD test.

B. Optical Microscope Analysis

The wet samples of co-crystal are observed under optical microscope to observe the crystal morphology. The crystal morphology also compared with the morphology of pure ibuprofen and citric acid crystal. Figure 2 shows the morphology of pure ibuprofen and pure citric acid. Figure 2(a) shows pure ibuprofen crystal grown tested with scale bar 100 μm has hexagonal plate-like shape (Abdur Rashid). Besides that, figure 2(b) shows pure citric acid also showed triangle and rectangular plate-like shape (Howey, 2015). Figure 2c) shows the experimental morphology of pure citric acid. The result shows that the shape is rectangular

plate-like shape and the same with the reference in the journal. Figure 3 shows the result for morphology of ibuprofen-citric acid co-crystal in ethanol solution while figure 4 shows the result for morphology of ibuprofen-citric acid co-crystal in propanol solution.

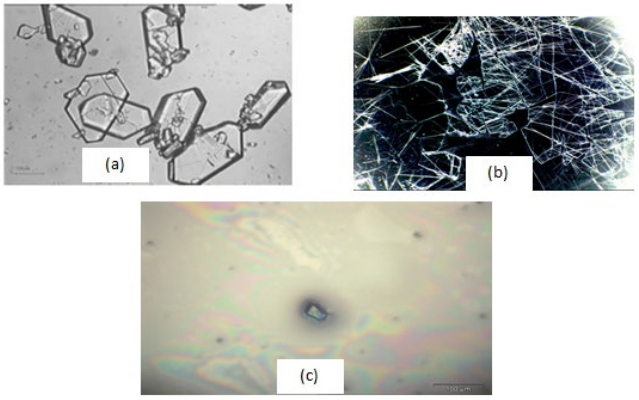


Figure 2 (a) Morphology of Pure Ibuprofen from Journal (Abdur Rashid), (b) Morphology of Pure Citric Acid from Journal (Howey, 2015), (c) Morphology of Citric Acid

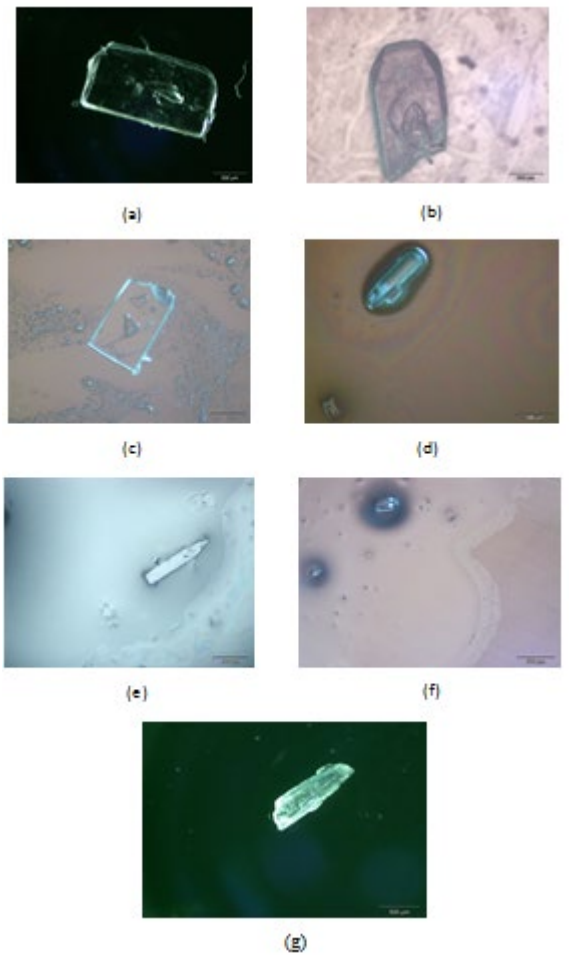


Figure 3 The Morphology of Cocrystal With Different Ratios in Ethanol Solution (a) 1:1 (500μm), (b) 1:1.5 (500μm), (c) 1:2 (200μm), (d) 1:2.5 (100μm), (e) 1:3 (100μm), (f) 1:3.5 (500μm) and (g) 1:4.5 (500μm)

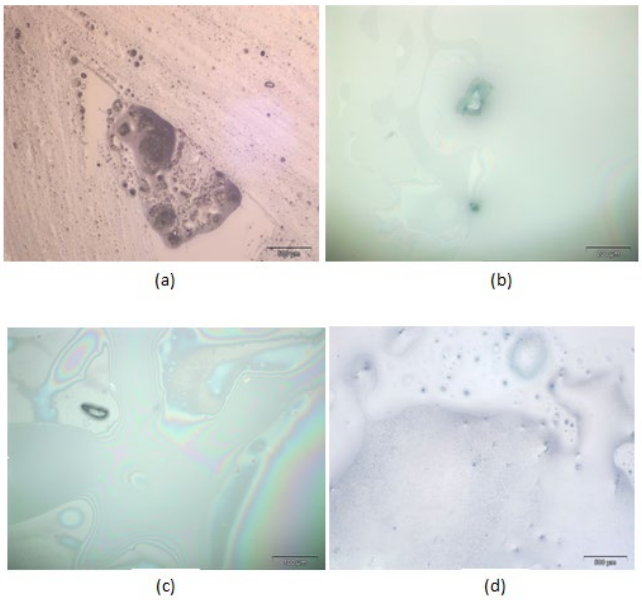


Figure 4 The Morphology of Cocrystal With Different Ratios in Propanol Solution (a) 1:2 (500μm), (b) 1:3(200μm), (c) 1:3.5 (100μm) and (d) 1:4 (500μm)

The morphology of the co-crystals formed also have plate-like shape but for the co-crystal in ethanol solution, the crystals size are bigger than the pure while in propanol solution, the crystals size are smaller than the pure ibuprofen and citric acid. The crystal formed in figure 4(d) is too small tills hard to identify the shape. According to H.A Garekani et.al in their research, crystallization of ibuprofen from ethanol, methanol, isopropanol, and hexane caused marked modifications to its crystal habit. The crystals growth is influenced by the type of solvent used. There is a large difference between the size distributions of ibuprofen crystal obtained from different solvent (H. A. Garekani, 2001).

B. Fourier Transform Infrared (FTIR) Analysis

Figure 5 shows the IR spectrum analysis of ibuprofen-citric acid in ethanol solution. The results are compared with the IR spectrum of pure ibuprofen and pure citric acid. Molecular structure of ibuprofen shows that ibuprofen has four functional groups which are carboxylic group, propyl group, aromatic ring and 2 methylpropylgroup (https://sites.google.com). Based on the figure 4 and table 2 for ibuprofen, the peak shows at 1542.04 cm^{-1} which is characterized as aromatic ring. Also a stretching of C=O of carboxylic acid group which have strong intensity of 1700.77 cm^{-1} is read added with medium broad intensity of O-H stretching at 2867.90 cm^{-1} indicates the carboxylic acid. At 2954.19 cm^{-1}, C-H stretching vibration is obtained.

Next, that the structure of citric acid is consists of a carbon atom bonded to two oxygen atoms, one through a double bond and one through the single bond with the latter oxygen atom also attached to a hydrogen atom thus it is a carboxylic acid functional group. This functional group appears 3 times in citric acid structure (Beauty by the Geeks, 2014). The IR spectrum for citric acid shows high intensity of 1692.94 and 1743.42 cm^{-1} for carboxylic acid group with C=O stretching vibration. A medium broad intensity of O-H stretching at 3282.99 cm^{-1} indicates the carboxylic acid and 3493.52 cm^{-1} for alcohol functional group. At 3282.99 cm^{-1}, C-H stretching vibration is also obtained.

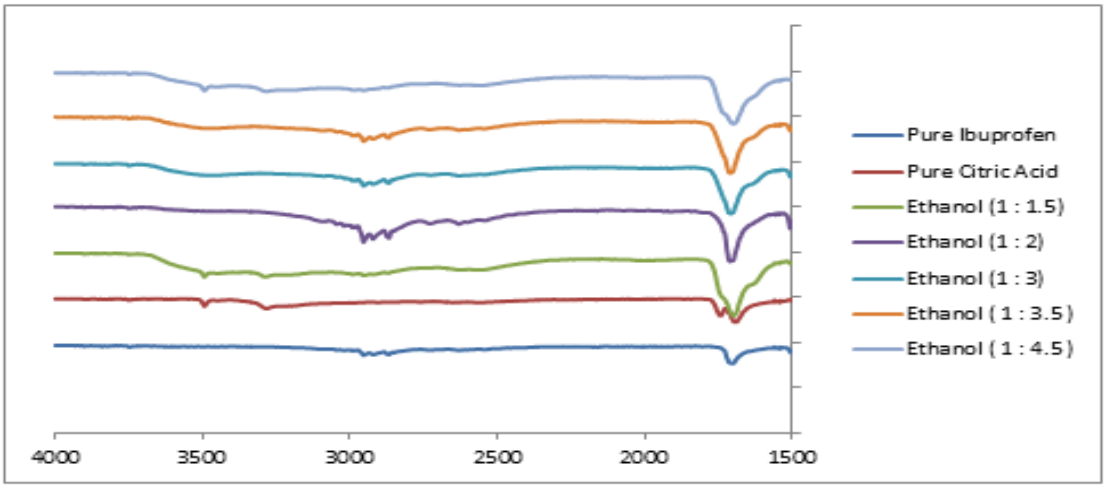


Figure 5 IR Spectrum Analysis for Ibuprofen-Citric Acid in Ethanol Solution

Table 2 Summary of FTIR Analysis in Ethanol Solution

Type of Bond	Wavenumber	Pure Ibuprofen	Pure Citric Acid	1 : 1.5	1:2	1 : 3	1:3.5	1 : 4.5
Aromatic Ring	1600 & ~1500-1430	1506.96			1507.70, 1556.44		1507.60, 1542.09, 1556.46	
C = O	1780 - 1650	1700.77	1692.94, 1743.42	1699.87	1709.88	1710	1709.10	1699.31
O – H (Alcohol)	3650 – 3200		3282.99, 3493.52	3494.07			3463.02, 3750.60	3284.42, 3493.29
O – H (Carboxylic Acid)	3300 - 2500	2867.90	3282.99	2580.63, 2953.74, 3287.12	2631.01, 2728.88, 2868.57	2874.12, 2999.76, 2945	2629.73, 2868.58, 2921.92,	2557.92, 2954.75,3284.42
C - H	3300 – 2700	2954.19	3282.99	2953.74, 3287.12	2922.05, 2954.36, 2991.60	2874.12, 2999.76, 2945	2954.26, 2990.90	2954.75, 3284.42

IR spectrum of ibuprofen-citric acid at 1:1.5, 1:3 and 1:4.5 ratio in ethanol solution shows that the aromatic ring functional group for ibuprofen at 1542.04 cm^{-1} is not exist. At ratio 1:2 and 1:3.5, the peak shifted from 1542.04 cm^{-1} to 1507.70 and 1507.60 cm^{-1} respectively. Besides that, the result also shows that there is a shift of the ibuprofen C=O stretching vibration band from 1700.77 cm^{-1} to 1699.87, 1709.88, 1710, 1709.10 and 1699.31 cm^{-1} for ratio 1:1.5, 1:2, 1:3, 1:3.5 and 1:4.5 respectively. All of the ratios also show the O-H stretching vibration for carboxylic acid group. At ratio 1:1.5, 1:3.5 and 1:4.5, there is O-H stretching vibration indicates alcohol functional group although ibuprofen does not have O-H bond for alcohol. Thus, these ratios have followed the nature of citric acid as it has alcohol functional group at 3493.52 cm^{-1}. But, there are slight changes at the O-H vibration at each ratio which are 3494.07, 3463.02 and 3493.29 for ratio 1:1.5, 1:3.5 and 1:4.5 respectively. Overall, there are shifted of peak occurred in all of the ratios mainly involved the aromatic ring and carboxylic acid group of ibuprofen and also in the O-H alcohol group in citric acid. Also, there is no new functional group detected in each of the ratio whenever compared with pure ibuprofen and citric acid.

From figure 5 and table 3, we can see that the aromatic functional group of ibuprofen not exists from all of the ratios. . Besides that, the result also shows that there is a shift of the ibuprofen C=O stretching vibration band from 1700.77 cm-1 to 1704.39, 1740.10 and 1708.66 cm-1 for ratio 1:2, 1:3 and 1:3.5 respectively. All of the ratios also show the O-H stretching vibration for carboxylic acid group with some shift of peak. All of the ratios have O-H stretching vibration for alcohol functional group although ibuprofen does not have O-H bond for alcohol. Thus, these ratios have followed the nature of citric acid as it has alcohol functional group at 3493.52 cm-1. However, there are slightly changes at the O-H vibration at each ratio which are 3494.30, 3494.91and 3444.40 for ratio 1:2, 1:3. and 1:3.5 respectively. Overall, there are shifted of peak occurred in all of the ratios mainly involved the aromatic ring and carboxylic acid group of ibuprofen and also in the O-H alcohol group in citric acid. Also, there is no new functional group detected in each of the ratio whenever compared with pure ibuprofen and citric acid.

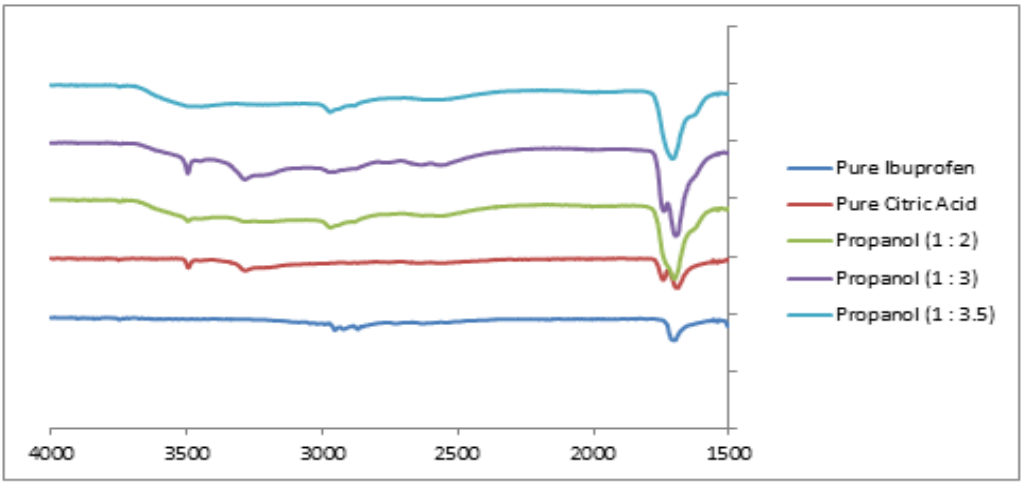


Figure 5 IR Spectrum Analysis for Ibuprofen-Citric Acid in Propanol Solution

Table 3 Summary of FTIR Analysis in Propanol Solution

Type of Bond	Wavenumber	Pure Ibuprofen	Pure Citric Acid	1 : 2	1 : 3	1 : 3.5
Aromatic Ring	1600 & ~1500-1430	1506.96				
C = O	1780 - 1650	1700.77	1692.94, 1743.42	1704.39	1697.47, 1740.10	1708.66
O – H (Alcohol)	3650 – 3200		3282.99, 3493.52	3494.30, 3742.89	3284.30, 3494.91	3444.40
O – H (Carboxylic Acid)	3300 - 2500	2867.90	3282.99	2559.69, 2696.01	2563.15, 2955.05, 3284.30	2970.20
C - H	3300 – 2700	2954.19	3282.99	2696.01	2955.05, 3284.30	2970.20

C. Differential Scanning Calorimetry (DSC) Analysis

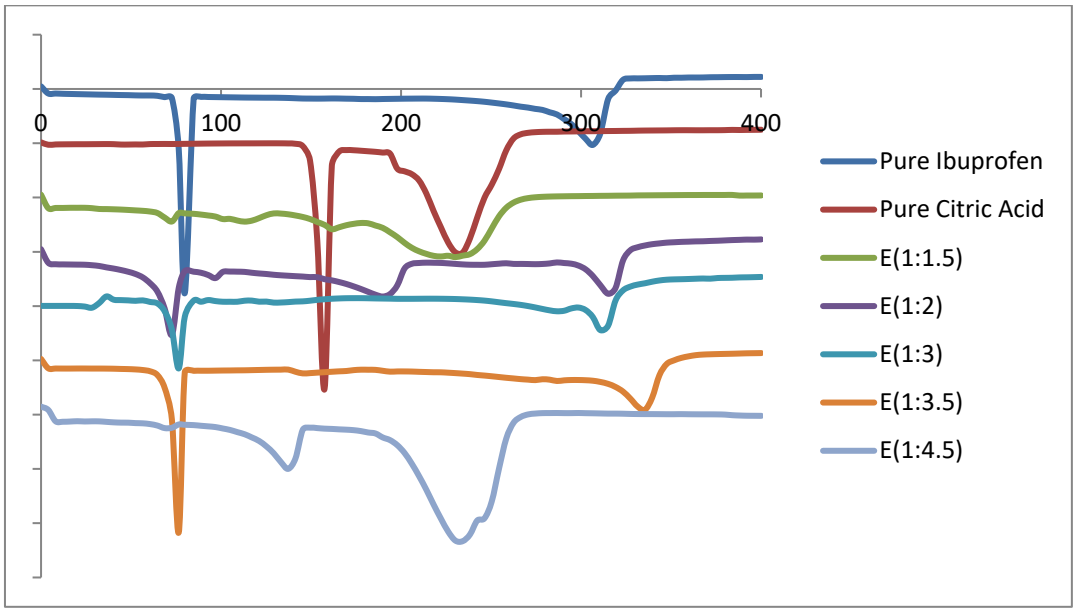


Figure 6 Differential Scanning Calorimetry Analysis in Ethanol Solution

Table 4 Differential scanning Calorimetry in Ethanol Solution

Name of Compound	Reported Melting Point of Individual Components (℃)	Ratio of Ibuprofen-Citric Acid	Reported Melting Point of Each Ratio (℃)
Ibuprofen	79.03, 307.63		
Citric Acid	156.36, 231.76		
		1 : 1.5	71.56, 113.87, 161.79, 234.51
		1 : 2	74.25, 96.02, 190.84, 316.25
		1 : 3	78.45, 312.90
		1 : 3.5	76.20, 334.50
		1 : 4.5	137.50, 232.62

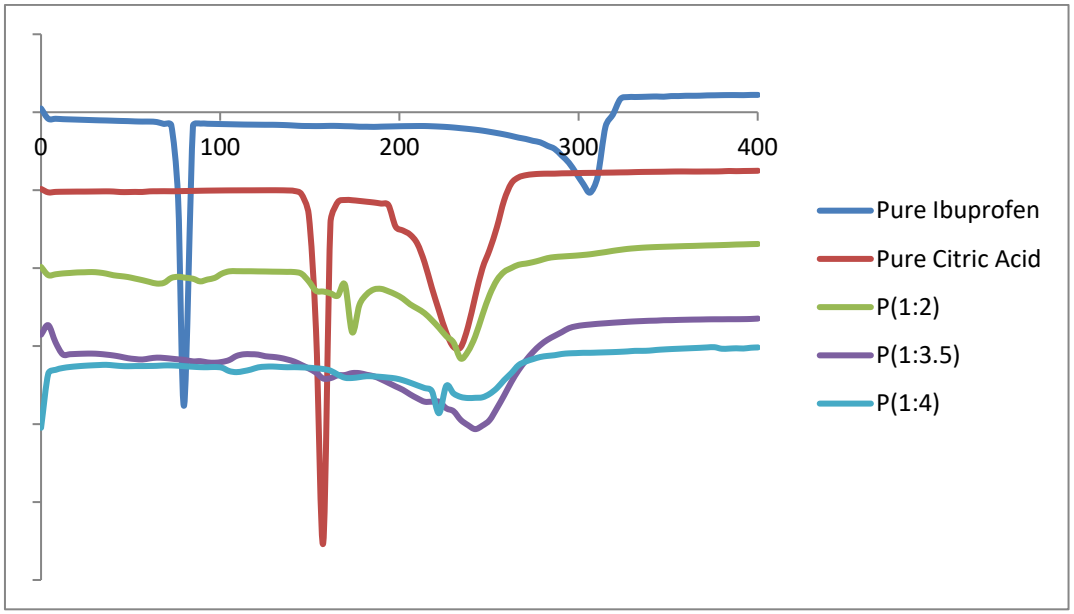


Figure 7 Differential Scanning Calorimetry Analysis in Propanol Solution

Table 5 Differential scanning Calorimetry in Propanol Solution

Name of Compound	Reported Melting Point of Individual Components (℃)	Ratio of Ibuprofen-Citric Acid	Reported Melting Point of Each Ratio (℃)
Ibuprofen	79.03, 307.63		
Citric Acid	156.36, 231.76		
		1 : 2	65.62, 88.12, 172.49, 232.14
		1 : 3.5	157.43, 243.14
		1 : 4	222.39, 246.99

DSC curve patterns of Ibuprofen, citric acid and ibuprofen-citric acid in ethanol solution are shown in Figure 6. A DSC curve of pure ibuprofen has shown an endothermic peak attributed a melting around 79.03℃. At a higher temperature, an endothermic peak appeared at temperature 307.63 ℃ due to thermal decomposition of ibuprofen (Safaa M Yousif1, 2016). The endothermic peaks of citric acid melting point are obtained at 156.36 and 231.76℃. The present of two endothermic peaks of citric acid refer to a change in the physical state, indicating the process of decomposition caused by high temperature (Mitchell, 1998).

For ratio 1:1.5, ibuprofen-citric acid mixture has formed due to an endothermic event around 234.51℃ due to the melting point of citric acid. Next, for ratio 1:2, the endothermic peaks also showed ibuprofen-citric acid mixture. Ibuprofen-citric acid mixture formed at temperature 74.25℃. At ratio 1:3 and 1:3.5, the melting point follow the pure ibuprofen at 78.45 and 76.20℃ respectively. Ibuprofen-citric acid physical mixture shows a complex thermal behaviour at ratio 1:4.5. An endothermic event around 232.62℃was due to melting of citric acid, and another endothermic peak was around 137.50℃ resulting from the melting of newly formed ibuprofen-citric acid co-crystal under DSC heating.

Figure 7 shows DSC analysis for ibuprofen-citric acid in propanol solution. All of the ratios have endothermic peaks that indicated the ibuprofen-citric acid mixture with unstable thermograph due to the citric acid melting. At ratio 1:2, the endothermic peaks showed at 172.49 and 232.14℃. Besides that, citric acid formed at temperature 243.14 and 222.39℃ for ratio 1:3.5 and 1:4 respectively.

IV. Conclusion

The co-crystallization of ibuprofen-citric acid has been conducted using slow-cooling method. The phase transformation assessment of ibuprofen-citric acid co-crystal in ethanol and propanol solution has been conducted and the formations of ibuprofen-citric acid samples were analyzed using DSC, FTIR and optical microscope. However, the crystals are not form for all of the ratios. The result of optical microscope shows that all of the crystal form has same shape with pure ibuprofen, plate-like shape but different size. Also no new functional group is identified whenever test using FTIR. Result from DSC test shows that all of the crystals formed are mixture instead of co-crystal. As the conclusion, slow-cooling method is not suitable for ibuprofen-citric acid co-crystal.

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