Study on Cocrystal Formation between Ibuprofen and Glutaric acid via Slow Evaporation Technique

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Abstract **– Ibuprofen is a non-steroidal anti-inflammatory drugs (NSAID) widely used in pharmaceuticals to treat pain. Pharmaceutical industries have been suffering from solubility issues which affect the delivery efficiency of the drugs. Hence, various methods have been done to enhance the solubility of active pharmaceutical ingredients (API). Cocrystallization has become a novel method in increasing solubility and stability of APIs. This research would like to discuss the cocrystallization study between ibuprofen (pure drug) and glutaric acid (co-former) via slow evaporation technique. Mixing of ibuprofen and glutaric acid with 1:1 molar ratio in propanol solvent were done with five molar ratio starting from 0.5 to 2.5 mole with step size of 0.5. The solutions were then heated until they were fully solubilized and left at temperature room for slow evaporation. Characterization of the cocrystals formed are done using optical microscope (OM), Fourier transform infrared spectroscopy (FTIR), differential scanning calorimetry (DSC) and X-ray powder diffraction (XRD). Based on the OM results, the crystals formed possessed plate shape which is the same with the pure shape of both ibuprofen and glutaric acid. Whereas, the FTIR results showed that cocrystal of IBP:GA was formed due to presence of different bands in comparison with the pure components. The DSC and XRD results analysis were successfully done which reveals that cocrystals of IBP:GA were produced. In conclusion, the IBP:GA cocrystals were successfully formed through slow evaporation technique in propanol solvent.**

Keywords – Co-crystallization; Ibuprofen; Glutaric acid; slow evaporation; cocrystal

I. INTRODUCTION

Active Pharmaceutical Ingredients (API) are known as active chemical agent that delivers the effect of the substances into the body such as pharmaceutical drugs. However, less than 40% of these drugs are water soluble [1] which means pharmaceutical drug developers are still facing the low solubility drug dilemma. Therefore, various methods have been developed in order to enhance the APIs solubility which includes micronization (lessening of particle size), solid dispersion with appropriate hydrophilic transferors, nanosuspension and micellar solubilization [1]. Yet, the exact physicochemical properties of the studied molecules defines the success of the methods stated above [2]. Hence, designation of pharmaceutical cocrystals has been a growing interest following this few decades.

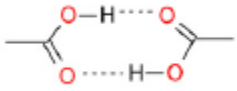
Pharmaceutical cocrystal can be defined as multi-component crystal that consists of two or more solid compounds under ambient condition [3] where at least one of the compound is neutral API and the co-former is pharmaceutically accepted ion or molecules. Cocrystallization has become a promising technology used nowadays to enhance the solubility, bioavailability and stability of most of the APIs. Where drug molecules are more stable, reproduceable and amendable to purification, cocrystallization is the best approach to overcome issues in pharmaceutical drugs.

Cocrystallization is done by combining an API with a suitable coformer where they interact through supramolecular hydrogen bonding, whether it is heterosynthon or homosynthon arrangement. Supramolecular heterosynthons are a non-covalent bond between distinct but complementary functional groups [4]. The functional groups include amides, alcohols and carboxylic acids. Supramolecular heterosynthons which are mostly favored to occur [4] can be integrated through slow evaporation method, sublimation and the newly developed effective method, solvent-drop grinding.

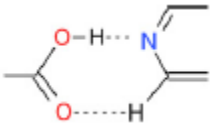
Cocrystals are designed through the intermolecular interactions which leads to the formation of supramolecules theory. The supramolecules formed later will have a novel structure and improved properties compared to the pure API compound. Better understanding of supramolecular chemistry of the listed functional groups is vital as it is a deciding factor in selection of suitable co-formers. The understanding of crystal engineering is facilitated by the Cambridge Structural Database (CSD) along with the APIs nature properties that is the availability of the external functional groups to participate in hydrogen bonds formation [4].

Supramolecular synthon term is frequently utilized in cocrystal formation practice where it is well-defined as supramolecular structural units that can be shaped through the synthetic method known which consist of intermolecular interactions [2]. Synthons are build up from distinct neutral

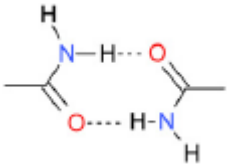
molecular species that exists as solids at ambient temperature [5]. Few familiar synthons that are generally found are shown in Figure 1 below.



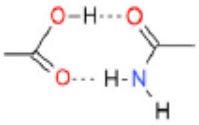
(a) Carboxylic homosynthon



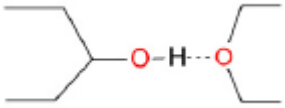
(b) Carboxylic acid – pyridine heterosynthon



(c) Amide – amide homosynthon



(d) Carboxylic acid – amide heterosynthon



(e) Alcohol – ether heterosynthon

Figure 1. Commonly found supramolecular synthons in crystal engineering [2]

Based on the Figure 1 above, supramolecular synthons can be divided into two types which are supramolecular homosynthon and heterosynthon. Homosynthon comprises of two molecules with similar self-complementary functionalities such as shown in Figure 1 (a) and (c). Whereas Figure 1 (b), (d) and (e) shows the examples for supramolecular heterosynthons that are buildup of unalike but complementary functionalities [6].

The cocrystals formed must be characterized in order to identify their properties whether they exist as a new compound or not. Numerous methods are developed and used in characterizing the cocrystal properties such as powder X-ray diffraction (PXRD), infrared spectroscopy (IR), Raman spectroscopy, Differential Scanning Calorimetry (DSC) and scanning electron microscopy (SEM).

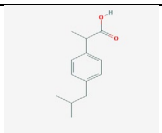
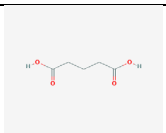
II. MATERIALS AND METHODS

A. Materials

Ibuprofen (isobutylphenylpropionic acid) is a non-steroidal anti-inflammatory drug categorized in BSC Class II drugs which has low solubility, high permeability properties. It is widely used to treat pain, fever and inflammation. This chemical was purchased from Sigma-Aldrich (China) and the purity was ≥99%. The chemical was used directly without further purification.

Glutaric acid (pentanedioic acid) is widely used in pharmaceutics and also industries use. GA has been used as virucidal agent in pharmaceutical industry [7] as well as adsorbents, absorbents and plasticizers in industry uses. The chemical (CAS-No. 110-94-1) was purchased from Merck Sdn. Bhd. (Selangor) with purification of ≥99%. The chemical was used directly without further purification.

Table 1. Chemical properties of studied compounds [7-10]

Compound	Ibuprofen	Glutaric acid
Structure		
Empirical formula	$C_{13}H_{18}O_2$	$C_5H_8O_4$
Molecular weight (g/mol)	206.2808	132.115
Melting point (°C)	75 - 77	97.5 - 98
Boiling point (°C)	157	200
Solubility in propanol (g/100g)	79.38	-
Solubility in water (mg/L)	21	1600000

B. Methodology

Preparation of ibuprofen and glutaric acid solution in propanol solvent

Five molar ratio of ibuprofen and glutaric acid solutions with 1:1 compound ratio were prepared starting from 0.5 to 2.5 with step size of 0.5. The amount of ibuprofen used were kept constant with varying the amount of glutaric acid used. Both of the chemicals were mixed in 20 mL vial with 5 mL propanol.

Table 2. Amount of Ibuprofen and Glutaric acid used for each molar ratio in propanol solvent

Mol ratio (IBP : GA)	Mass IBP (g)	Mass GA (g)
1.0 : 0.5	1.98	0.63
1.0 : 1.0	1.98	1.27
1.0 : 1.5	1.98	1.90
1.0 : 2.0	1.98	2.54
1.0 : 2.5	1.98	3.17
1.0 : 3.0	1.98	3.81
1.0 : 3.5	1.98	4.44
1.0 : 4.0	1.98	5.07
1.0 : 4.5	1.98	5.71

Slow Evaporation Technique

The vials containing IBP:GA solution were placed into orbitary shaker for heating. Water bath was used to raise and maintain the temperature during the heating process. The working temperature and speed of the orbitary shaker were 60°C and 250 rpm respectively. The heating process continued for three hours until all the solutes were completely dissolved. After clear solutions from all the samples were obtained, the vials were removed from the orbitary shaker and placed on a bench at room temperature. The vials were covered with aluminium foils that have been made several holes to allow evaporation to take place.

Optical Microscope (OM) Characterization

Optical microscope was used to observe the morphology of the crystals formed. OLYMPUS DP72 microscope was used. The morphology analysis was done by examining the slurry sample under the microscope with different magnifications. The shape of cocrystals was compared with the pure compounds.

Figure 2. Meiji Techno 1559 optical microscopy

Fourier Transform Infrared Spectroscopy (FTIR) Characterization

The pure drug, co-former and cocrystals infrared spectra were obtained. The samples were run at spectral resolution of 2 $^{cm-}$1. FTIR was used to analyze the compound and bonding present in the crystal formed. It was also used to determine type of crystals formed. FT-IR Spectrometer from Perkin Elmer (Figure 2) was used with wavelength operated from 500 to 4000 cm^{-1}.

Figure 3. FT-IR Spectrometer from Perkin Elmer

Figure 4. DSC 820 Mettler Toledo

Differential Scanning Calorimetry (DSC)

DSC was used to perform thermal analysis of IBP, GA and IBP:GA cocrystal. The analysis was performed with DSC 820 Mettler Toledo with temperature ranging from 0 - 400°C using nitrogen gas and at the rate of 4°C per minute.

X-ray Powder Diffraction (XRD)

X-ray Diffraction was used to determine peak pattern of the new compound through the computational data displayed by the XRD. In order to make sure the sample is in powder form, the sample was grinded using pestle and mortar before being analyzed. This equipment operates at voltage of 40 kV and current at 40 MA. The speed angle was set at 1.5° with start angle at 3 and ended at 40 degrees. The minimum step size used is 2Theta:0.02.

Figure 5. XRD used to determine new crystalline structure in cocrystals

III. RESULTS AND DISCUSSION

Cocrystallization study was conducted between ibuprofen and glutaric acid with 1:1 molar ratio through slow evaporation technique. The cocrystallization was done in propanol solvent and cocrystals characterizations were performed using OM, FTIR, DSC and XRD.

The morphology of cocrystals formed were compared with the morphology of pure ibuprofen (Figure 6a) and glutaric acid (Figure 6b). It was observed that the IBP:GA

cocrystals possessed plate-shaped crystal just as the pure components' shape.

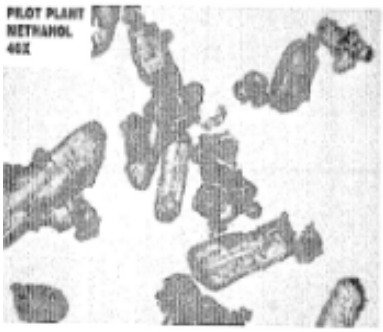


Figure 6a. Plate-shaped crystal of pure Ibuprofen [11]

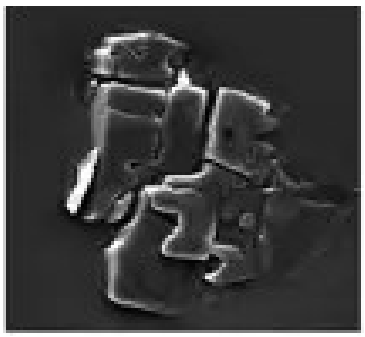
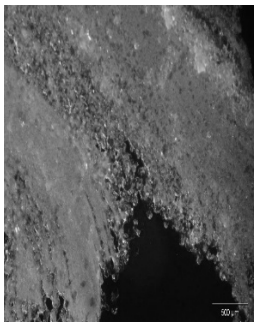
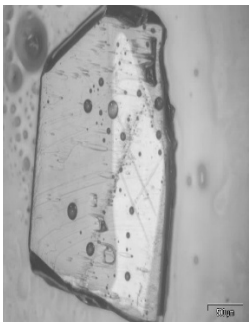


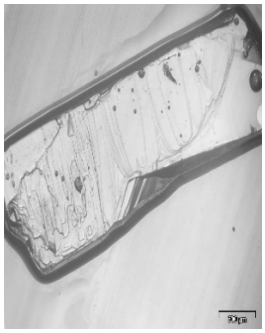
Figure 5b. Plate-shaped crystal of pure glutaric acid [12]



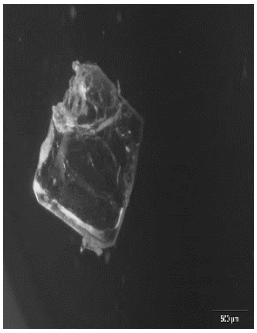
(a)



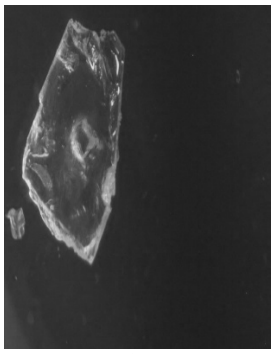
(b)



(c)



(d)



(e)

Figure 7. OM results for IBP:GA cocrystals (a) 1.0:0.5 (b) 1.0:1.0 (c) 1.0:1.5 (d) 1.0:2.0 (e) 1.0:2.5

Data obtained from FTIR spectroscopy were studied in order to evaluate whether the complex forms cocrystal or not. This can be determined by observing any shifting of peaks from the pure drug and co-former studied. Ibuprofen contains aromatic functional group (C=C) at 1575.1, carbonyl bond (C=O) at 1721 cm, alcohol bond (O-H) at 3357.54 and alkane bond (C-H) at 2922.03. Glutaric acid contains carbonyl group (C=O) at 1697, acid group (O-H) at 2704 and alkane group (C-H) at 2954. Meanwhile, peak attributed to C=C stretch has been shifted to 1507, peak for C=O stretch shifted between 1721 and 1697, peak for acid group O-H shifted to 2727 and peak for C-H stretch shifted to 2632 until 2991 (Figure 8 and Table 3). Whereas, there was no peak for alcohol group O-H stretch observed in cocrystals spectrum. C=C aromatic bond and O-H alcohol group were observed in the cocrystal samples eventhough the bonds were absent in glutaric acid and O-H acid group was also present in the ibuprofen-glutaric acid cocrystals though there was none in ibuprofen. These results indicated that both pure drug and the co-former are present in the new cocrystal compound.

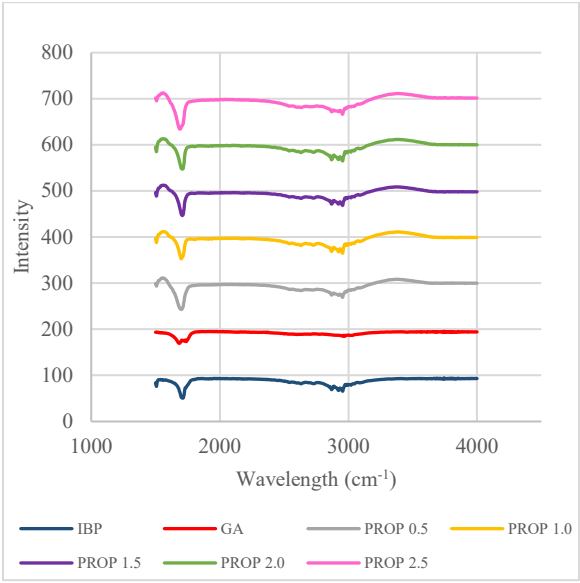


Figure 8. FTIR results for IBP:GA cocrystals

Table 3. Comparison of FTIR spectrum analysis of IBP, GA and cocrystals

Functional group assigned to	IBP	GA	IBP:GA
C=C stretch of aromatic	1575.1	-	1507
C=O stretch of carbonyl	1721	1697	1700
O-H stretch of alcohol	3357.54	-	-
O-H stretch of acid	-	2704	2727
C-H stretch of alkane	2922.03	2954	2632 - 2991

Differential Scanning Calorimetry (DSC) thermal analysis showed endothermic peak at 78.27°C for ibuprofen which verified the melting point range stated in Table 1. Glutaric acid showed two endothermic peaks at 74.91°C and 96.87°C. All five samples of cocrystals showed endothermic peaks melting point as listed in Table 4. All endotherm melting peaks for cocrystal samples are located between melting point of pure ibuprofen and pure glutaric acid except for molar ratio of 1.0:0.5 which is smaller compared to the melting point of ibuprofen (Figure 9). This is due to the unstable cocrystal formed during the process. It can be seen that the lower mole ratio of cocrystals exhibited close melting point value with that of ibuprofen whereas higher mole ratio of the cocrystals exhibit melting point value close to the glutaric acid's. Thus, it can be concluded that the melting point of cocrystals increases as the molar ratio increases. New peak location for the cocrystal samples indicates that a new compound which is IBP:GA cocrystal was formed. Nevertheless, these outcomes suggested a complete formation of ibuprofen-glutaric acid cocrystals.

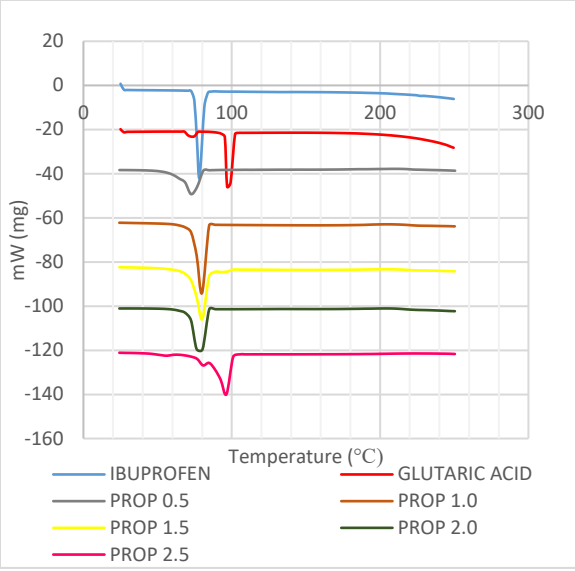


Figure 9. DSC analysis of ibuprofen-glutaric acid cocrystal

Table 4. Peaks location for DSC analysis result

Compound	Peak (s) location (°C)	Condition
Ibuprofen	78.27	-
Glutaric acid	74.91 and 96.87	-
IBP:GA (1.0:0.5)	72.51	Unstable
IBP:GA (1.0:1.0)	79.96	Stable
IBP:GA (1.0:1.5)	80.16	Stable
IBP:GA (1.0:2.0)	80.32	Stable
IBP:GA (1.0:2.5)	96.43	Stable

XRD analysis was performed to determine the crystallography structure of the new cocrystals. There were several new peaks formed in XRD analysis results (Figure 10). A peak was formed at 6.1° for all five cocrystal samples which is the same peak formed in ibuprofen which was at 6.4 whereas no peak observed in glutaric acid in that region. At 12.25°, there were peaks formed for the cocrystal samples which followed the peak formed in ibuprofen at 12.64°. There were also peaks formed at 13.84° for all five cocrystals which reflected the peak formed in glutaric acid at 13.86°. However, there were new peaks formed in the cocrystals which were at 20.2° which is between ibuprofen's and glutaric acid's peaks at 20.5° and 19.66° respectively. There were also new peaks observed at 22.35° in the cocrystal where the peak for ibuprofen was at 22.46° and at 20° for glutaric acid. Besides, new peak was also observed at 35.45° where none of the pure compounds showed peaks. Based on these new peaks observed, it can be said that formation of ibuprofen-glutaric acid cocrystal has succeeded.

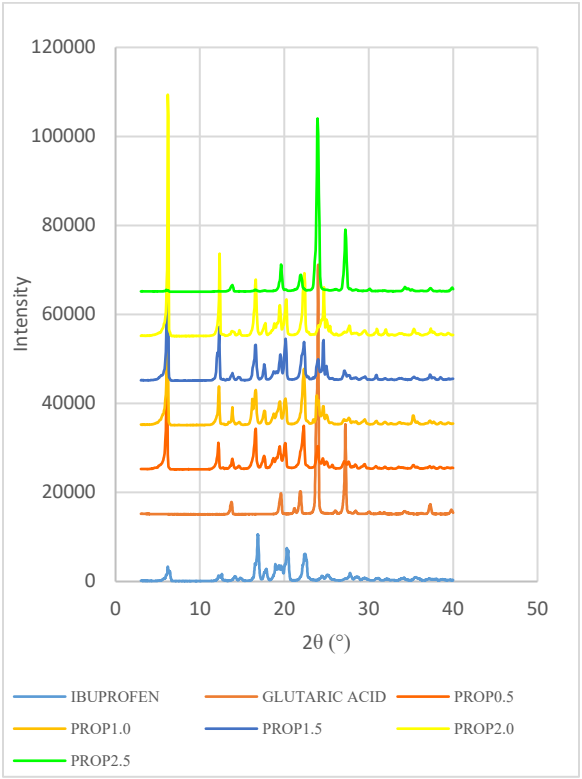


Figure 10. XRD results analysis for IBP:GA cocrystals

Table 5. New peaks observed from XRD analysis of ibuprofen-glutaric acid cocrystals

Molar ratio (IBP:GA)	New peaks (°)			
1.0:0.5	20.2	22.35	25.8	35.35
1.0:1.0	20.21	22.5	25.8	35.4
1.0:1.5	20.2	22.4	25.75	35.45
1.0:2.0	20.3	22.45	25.5	35.5
1.0:2.5	19.7	22	25.65	35.25

IV. CONCLUSION

The aim of this work was to study the cocrystallization between ibuprofen and glutaric acid via slow evaporation technique. Five molar ratios were used with step size of 0.5 starting from 0.5 to 2.5 in propanol solvent. Characterization of the crystals formed were done using OM, FTIR, DSC and XRD. Based on OM results obtained, the IBP:GA cocrystals possessed plate-shaped crystal which are the same with the morphology of pure ibuprofen and glutaric acid. Whereas the FTIR results showed that IBP:GA crystals had several bonds shifted from the original compounds which suggested ibuprofen-glutaric acid cocrystal has been formed. The DSC results showed new endothermic melting peaks in the five cocrystal samples. Lastly, the powder XRD analysis resulted in new peaks formation as tabulated in Table 5. Hence, it can be concluded that cocrystal of ibuprofen-glutaric acid has been successfully done and all the experimented mole ratios were suitable to be performed.

ACKNOWLEDGMENT

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