Study on Co-crystal Formation of Ibuprofen and Glutaric Acid via Slow Cooling Technique.

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***Abstract*—Ibuprofen is non-steroidal anti-inflammatory drug (NSAID) that used to treat pain or inflammation and to reduce fever. It is fall under Biopharmaceutical Classification System (BCS) Class II which has low solubility but high permeability. In order to improve the bioavailability of ibuprofen, an engineering approach has been done. For that purpose, an engineering crystal approach is done by preparing the co-crystal of ibuprofen and co-former such as glutaric acid to help in improving drug solubility. The method used to prepare the co-crystal is slow cooling technique. Using this technique, there are several samples of ibuprofen-glutaric acid that successfully to perform co-crystal. The successful samples were characterized using Fourier Transform Infrared Spectroscopy (FTIR), Differential Scanning Calorimetry (DSC) and optical microscope in order to confirm their morphology and purity. The findings from the study shows that the result of FTIR shows that there is new bond formed from the interaction of ibuprofen and glutaric acid. The result from DSC showing that there is formation of new melting point in between pure component used in this experiment. Lastly, the optical microscope had successfully identify the morphology that revealed by the co-crystals.**

***Keywords*—** *Co-crystal, Glutaric Acid, Ibuprofen, and Slow Cooling Techniques.*

I. INTRODUCTION

Co-crystallization is a technique that used to improve the physicochemical properties of an active pharmaceutical ingredient (API). Ibuprofen is a non-steroidal anti-inflammatory drug (NSAID) that is usually used as pain relieve medicine or to reduce fever. However, it falls under BCS Class II which has low solubility limitation in gastrointestinal tract despite its high permeability. According to world health organization (WHO) guideline, active pharmaceutical ingredients (APIs) can be defined as any material or mixture of materials used in a finished pharmaceutical product (FPP), intended to supply pharmacological activity to have direct effect in the diagnosis, cure, mitigation, treatment or prevention of disease, or to have direct effect in restoring, correcting or modifying physiological functions in human beings (Kopp, 2011). Alteration of the physicochemical properties of a crystalline active pharmaceutical ingredients (APIs) by introducing a pharmaceutically suitable compound is a present strategy in drug formation and dosage optimization (Sanphui, et al., 2012).The use of co-crystal technology in active pharmaceutical ingredient (API) crystallizations is an allowing technology to bring improve pharmaceutical products to the market place as well as for the improved drug delivery (Jasud, et al., 2013). While for the definition of co-crystal, it has become a debate among the scientists. There are many terms used to give a definition to co-crystal. Up until now, there is no specific definition can be used to precise the meaning of co-crystal.The definition of co-crystal suggested by Aekroy, where co-crystal alignment from supramolecular synthons is to take account of forming from discrete neutral molecular species that are solid at ambient temperatures, where the co-crystal is an arrangement homogenous crystalline material that holds the building blocks definite stoichiometric amounts (Brittain, 2012).

Ibuprofen (IBP) is a nonsteroidal anti-inflammatory drug (NSAID) that is widely used for their anti-inflammatory, antipyretic and analgesic properties in the treatment of arthritis, antipyretic and analgesia (Sun, et al., 2014). The IUPAC name of Ibuprofen is 2-(4-(2-methylpropyl)-phynyl) propanoic acid (Anon., 2015). Ibuprofen is categorized under Biopharmaceutics Classification System (BCS) class II drug with low solubility at pH 1.2 and 4.5 and high solubility at pH 6.8.(Sun, et al., 2014). According to Bronstein 2004, the oral absorption of ibuprofen is usually good as ibuprofen rapidly absorbed from the gastrointestinal (GI) tract with peek concentrations achieved in 15 to 30 minutes. The author also stated that, though the absorption is high the solubility of ibuprofen is relatively low, which is being less than 0.1 mg/ml in water. This may cause the absorption of large ingestions to be limited. Ibuprofen is metabolized more than 99% and has two main hepatic metabolites which are either excreted as 2-hydroxyibuprofen and 2-carboxyibuprofen on their conjugates (Bronstein, 2004).

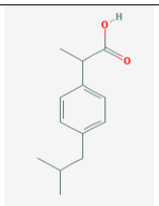
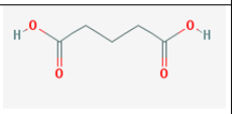
Ibuprofen has been reported to be able to form 1:1 cocrystal with nicotinamide (NCT), benzoic acid, 3-aminobenzoic acid and cinnamic acid. The solubility tests indicated that the aqueous solubility of IBP-NCT cocrystals is 7.5 times higher than that of pure Ibuprofen (Sun, et al., 2014) and Ibuprofen with benzoic acid showed the highest solubility which 7 times higher as compared to pure Ibuprofen, meanwhile cocrystal of Ibuprofen with 3-aminobenzoic acid and cinnamic acid showed comparably good solubility which are 3 times faster than pure Ibuprofen (Gangadhar, et al., 2014).

In order to produce co-crystallization, there are several factors that can give effect to it and they are types of solvent used, nucleation, mechanics, time and crystal growing techniques. Solvent is very important element to choose when trying to develop a cocrystal. A suitable solvent which usually have moderate solubility is chosen. This is because if the mixture can perform supersaturation conditions with solvent, it can produce sudden precipitation and smaller size of crystal. Besides that, nucleation factor also need to be concern. It is better if the nucleation sites are fewer because it will increase the average size of crystal. Basically, the nucleation condition occurs when the crystal is formed through nucleating events. Then, after the crystallite already has nucleated, it will grow. The nucleation sites are also important in crystallization however it must avoid too much excess to nucleation sites to prevent the smaller size of crystal. Mechanical factor also important because crystal grows in ordered deposition of the solute molecules onto surface of pre-

existing crystal. So any sources of mechanical agitation such as vibrations should be avoided. Next, the time also can bring effect towards co-crystallization. This is to produce best the quality of crystal. The last factor is related to crystal growing method. There are variety types of techniques that can be done to produce co-crystal. However, it depends on the condition of co-crystal to be occurred.

The scopes of research for this research project are includes the study of the formation of ibuprofen and glutaric acid cocrystal via slow cooling technique in order to improve the solubility of ibuprofen. In this research the solvent used is 1-propanol solvent. Before carried out the experiment of co-crystal formation of Ibuprofen and Glutaric acid via slow cooling techniques, some properties of Ibuprofen and Glutaric Acid are listed as table below.

Table 1: properties of Ibuprofen and Glutaric Acid.

	IBUPROFEN	GLUTARIC ACID
Chemical Names	2-[4-(2-methylpropyl)phenyl]propanoic acid	2-[4-(2-methylpropyl)phenyl]propanoic acid
Structure		
Molecular Formula	$C_{13}H_{18}O_2$	$C_5H_8O_4$ or $COOH(CH_2)_3COOH$
Molecular Weight	206.285 g/mol	132.115 g/mol
Melting Point	76-78 °C	95-98°C
Boiling point	157 °C	303°C
Density	1.03 g/ml g/cm^3	1.4 g/cm^3

The physical properties of ibuprofen and glutaric acid cocrystal are assessed through the characterization of crystal product using analytical instruments such as optical microscopy and FT-IR. The study of co-crystal formation of ibuprofen and glutaric acid is very important especially in pharmaceutical industry. By having cocrystal form especially for drugs, it can bring so many advantages to consumer. It can increase the performance of a dosage form especially for compound that having intrinsic barrier to delivery of drug. Usually the problem regarding to drug delivery are low aqueous solubility, slow dissolution in gastrointestinal media and others. So, due to this problem the application of crystal engineering such as cocrystal was used to enhance the solubility of drugs. By using cocrystal technique, it can alter the physicochemical properties of API besides maintaining the intrinsic activity of drug molecule. Next, cocrystal is a stable crystalline form which does not need to break or make covalent bonds and usually it capable to all types of API. Lastly, the solid form of crystal is able to produced using solid-state synthesis green technologies high yield.

II. METHODOLOGY

A. *Materials*

There are three main materials used in this experiment and they are Ibuprofen, Glutaric Acid and 1-propanol. Ibuprofen (IBP, MW = 206.28082 g/mol) was purchased from Shasun Pharmaceutical Limited, India (Batch No.: IB 11070248) (SN Grade). Glutaric acid (GA, MW = 132.11642 g/mol) was purchased from MERCK, Germany. 1-propanol (MW = 60.09502 g/mol) were purchased from Sigma-Aldrich, Germany. All compounds were used as received.

B. *Preparation of Ibuprofen-Glutaric Acid Co-crystal*

The preparation of Ibuprofen-Glutaric Acid co-crystal is done using slow cooling technique. Ibuprofen and Glutaric Acid were mixed in powder form based on the several stoichiometric ratio calculations (1: 0.5-4.5). Then, 5 mL of 1-propanol was added into the vial that containing mixture of Ibuprofen and Glutaric Acid. To make sure that the mixture of Ibuprofen and Glutaric Acid were totally dissolved in 1-propanol, the vials were placed on the orbital shaker and were heated up until 60°C and set at 250 rpm. After the compound already dissolved, the solutions were let for an hour to make them achieved the supersaturation phase. Then, the solutions were undergoes cooling process. The temperature for orbital shaker was cooled down until 20°C and run at 50 rpm. The cooling rate used for this experiment was 0.67°C/min. The formation of co-crystal was occurred when the solution had achieved the cooling temperature. The co-crystal formed was filtered using filter paper. The co-crystal obtained was allowed to dry until it completely dry. The co-crystal obtained was characterized using FTIR and optical microscopy.

C. *Optical microscopy*

The morphology of ibuprofen-glutaric acid co-crystals was observed using Olympus BX41 optical microscope that was equipped with software. In this study, the morphologies of wet product co-crystals were used to be observed under the optical microscope.

D. *Fourier Transform Infrared (FTIR)*

The co-crystal was characterized using FTIR spectroscopy (Thermo Nicolet 6700). This FTIR spectroscopy is used to identify the functional groups that present in the crystal. For each sample, scan is conducted in the range of 500 cm^{-1} to 4,000 cm^{-1}. In order to run FTIR spectroscopy, the plate to place the sample must be cleaned using acetone solution. Thus, the impurities that available around the plate can be removed.

E. *Differential Scanning Calorimetry (DSC)*

The co-crystal also was characterized by using DSC 820 (Mettler Toledo Inc.,Columbus, USA) under nitrogen gas flow of 10 mL/min. All the samples were in powder form. Before run the DSC, all the samples were weighed about 6-10 mg and put in the non-hermetic sealed aluminium pans. All the samples were analysed between 25°C to 250°C at heating rate of 10°C/min. The melting point for every sample was recorded.

III. RESULTS AND DISCUSSION

A. *The effect of solvent used*

In order to produce the co-crystal of ibuprofen-glutaric acid, it must use the help of solvent to make it dissolve. The 1-propanol is an alcohol that serves as solvent for the slow cooling co-crystallization process. In this research, the amount of solvent used is 5 mL. However, the amount of solvents used is depends on the calculation of ibuprofen and glutaric acid ratio. When the stoichiometric ratio is increased, the mixture becomes more hardly dissolved in the solvent. This shows that the amount of solvent used must be increased as the stoichiometric ratio of ibuprofen and glutaric acid is increased. So, it is important to use the correct amount of solvent so that it will make the mixture more easily to dissolve in the solvent.

B. *Fourier Transform Infrared Spectroscopy*

The FTIR results mainly involved in the shifting of C=C stretching aromatic ring, C=O stretching and O-H stretching of carboxylic acid functional group for ibuprofen and also at certain ratio for glutaric acid. The reading of the peak is taken from 1500 cm^{-1}.

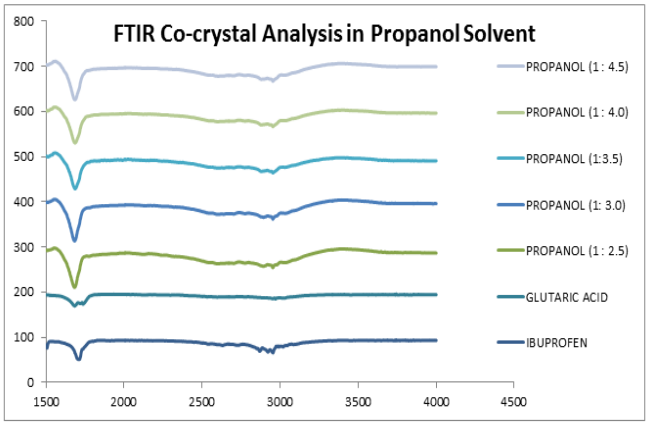


Fig 1: IR spectrum analysis of IBP-GA co-crystal in 1-propanol

Table 2: Characteristic IR spectrum absorption frequencies of IBP-GA co-crystal in 1-propanol.

FUNCT. GROUP	CHARACT. ABSORPTION	PURE IBUPROFEN	PURE GLUTARIC ACID	PROPANOL (1 : 2.5)	PROPANOL (1 : 3.0)	PROPANOL (1 : 3.5)	PROPANOL (1 : 4.0)	PROPANOL (1 : 4.5)
Alkyl C-H	2950 -2850	2992.17	2970.58	2893.84	2893.96	2880.05	2879.06	2879.64
Aromatic C=C	1700 – 1500	1506.97		1683.04	1683.63	1687.76	1687.34	1686.82
Carboxylic acid O-H	3000 – 2500	2632.03, 2727.24, 2992.17	2970.58	2953.49, 2893.84, 2606.50	2953.64, 2893.96, 2603.01	2954.04, 2880.05, 2606.50	2953.88, 2879.06, 2595.90	2954.02, 2879.64, 2606.67
Ketone C=O	1750 – 1680	1709.79	1683.90, 1738.84	1683.04	1683.63	1687.76	1687.34	1686.82
Amide C=O	1690 – 1630			1683.04	1683.63	1687.76	1687.34	1686.82

Fig. 1 and table 2 show the result of FTIR for ibuprofen-glutaric acid in the several ratios which are (1:2.5), (1:3.0), (1:3.5), (1:4.0) and (1:4.5). The samples of successful co-crystals then were compared with the pure component of ibuprofen and pure component of glutaric acid. Based on the fig 1, the sample of co-crystals showing almost the same peak as the pure component but there is only a slightly changed occur in several functional bond. In co-crystal of ibuprofen-glutaric acid that have ratio (1: 2.5) or stated as Propanol (1:2.5) in the table above, some observation had been made by comparing with ibuprofen and it shows that the C-H bond was shift from 2992.17 cm^{-1} to 2893.04 cm^{-1}. For C=C bond, there is a change occur which the absorption changes from 1506.97 cm^{-1} to 1683.04 cm^{-1}. Then,for O-H bond, the absorption is shifting from 2632.03 cm^{-1} to 2606.50 cm^{-1}. While, for C=O bond, the absorption occurs from1709.7 $9cm^{-1}$ to1738.84 cm^{-1}. Besides that, when comparing with glutaric acid, it only involved shifting of bond in three types of functional group which are C-H, O-H and C=O bond. For corystal with ratio 1: 2.5, there is also shifting of bond occurs. For example, for C=O bond, the absorption shift from 1638.90 cm^{-1} to 1683.04 cm^{-1}. Furthermore, there is almost the same result goes to the other sample of co-crystal which have ratio of (1:3.0), (1:3.5), (1:4.0) and (1:4.5). All of these samples also having the same situation as co-crystal with ratio of (1:2.5). There are absorption of bond shift occurs towards these sample when comparing with their pure component. Based on the observation made, there is no component of the co-crystal produced forming the same position exactly like their pure component. So, the IR spectrum of co-crystals result showed that there are evidences that there is alteration of the hydrogen bond schemes occur.

C. Differential Scanning Calorimetry

Differential Scanning Calorimetry (DSC) was used to characterize the sample of Ibuprofen-Glutaric Acid. The purpose of using DSC is to determine the thermodynamic transitions and heat capacities of substances. Through this analysis, the physical change that happens towards sample could be identified and at the same time, it can determine the purity of a substance. By setting the temperature range 25°C to 400°C and the heating rate of 10°C/min, all the samples data were recorded. The Fig. 3 below shows the data recorded for the sample and the samples were comparing with pure data of Ibuprofen and pure Glutaric acid.

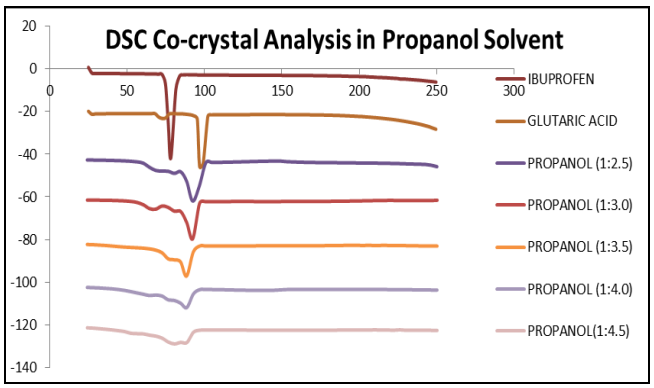


Fig. 3 : Analysis of DSC for IBP-GA co-crystal in 1-propanol.

According to the Fig. 3 above, there are different peaks for every sample was recorded. The sample of co-crystal above had been comparing with the result of pure Ibuprofen and pure Glutaric Acid. As mention in the earlier, the melting point for Ibuprofen is 76°C and the melting point for Glutaric Acid is range from 95°C to 98°C. (PubChem,2004) According to this experiment, the melting point of pure Ibuprofen was recorded at 78.27°C and the melting point for Glutaric Acid was recorded at 96.87°C. In order to see the result more clearly, the table of comparison between the co-crystal sample and the pure Ibuprofen and pure Glutaric acid had been prepared in Table 3 below.

Table 3 :Comparison of melting point for Co-crystal and their pure component.

Name of compound	Melting point of the individual components (°C)	Ratio of Cocrystal (IBP-GA) in1-propanol.	Reported melting point of the cocrystals components (°C)
Ibuprofen	76		78.27
Glutaric Acid	95-98		96.87
		1:2.5	92.34
		1:3.0	92.40
		1:3.5	88.44
		1:4.0	88.58
		1.4.5	88.67

Based on table above, all the samples for the co-crystal of Ibuprofen-Glutaric acid have melting point in between pure Ibuprofen and pure Glutaric acid. Based on the graph plotted, the co-crystal with ratio 1:2.5 have melting point at 92.34°C, co-crystal with ratio 1:3.0 have melting point at 92.34°C, co-crystal with ratio 1:3.5 have melting point at 88.44°C, co-crystal with ratio

1:4.0 have melting point at 88.58°C and co-crystal with ratio 1:4.5 have melting point at 88.67°C. So, from the result obtained from DSC above, it can be conclude that the samples are the co-crystals of Ibuprofen-Glutaric acid due to the formation of new sharp melting point of co-crystal in between the pure component which indicating the binary nature of the Co-crystal.

D. Morphology

The morphology that formed between Ibuprofen-Glutaric Co-crystal was analyzed using Olympus BX41 optical microscope. The morphology of pure Ibuprofen and pure Glutaric acid are shown in Fig 3. The morphology of co-crystals are observed and shown in Fig 4. From the observation under the optical microscope, the morphologies among the samples are different although they are mixed using the same Ibuprofen and Glutaric Acid but different molar ratio. The morphology of pure Ibuprofen is quite difficult to be predicted because it exhibits different morphologies when grown from different solvent. When ibuprofen grown from alcohol, it will shows plate shaped crystal and shows needle shaped crystal when grown from non-polar solvent. However, for glutaric acid, the morphology of it is plate like shape. In the fig 3, there are only several samples of Ibuprofen-Glutaric Acid that can be obtained from the experiment and all of them form a crystal at high molar ratio of the mixture. The sample of ibuprofen-glutaric acid that successfully became a crystal after mixed with propanol is start from ratio (1:2.5), (1:3.0), (1:3.5), (1:4.0) and (1:4.5). All of them showed different morphology as compared to the pure component.

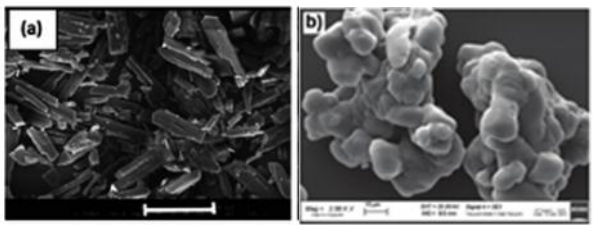


Fig. 3: a) pure Ibuprofen b) pure Glutaric Acid

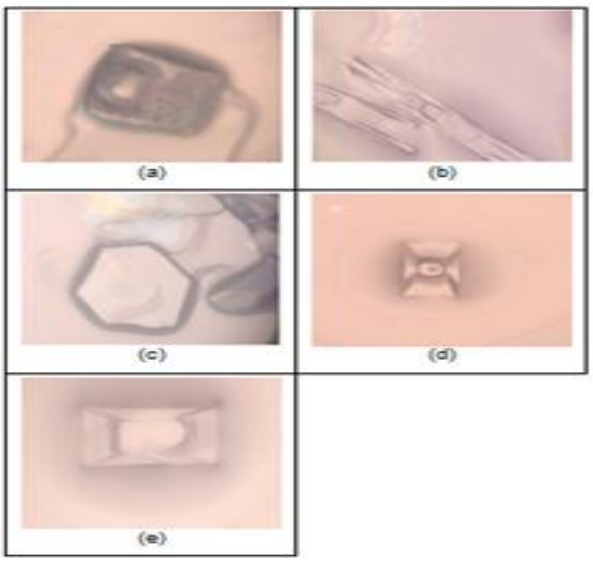


Fig. 4 : Morphology of the samples under optical microscope. (a) 1:2.5 ratio (Ibp:GA) (b) 1:3.0 ratio (Ibp:GA) (c) 1:3.5 ratio (Ibp:GA) (d) 1:4.0 ratio (Ibp:GA) (e) 1:4.5 ratio (Ibp:GA)

From the observation made according to the image of the samples under optical microscopy, the morphology of sample that have ratio (1:2.5), (1:4.0) and (1:4.5) are showing the same shape which is prism like shape while sample in ratio (1:3.0) shows elongated plate shape and the sample in ratio (1:4.0) shows hexagonal-like shape.

IV. CONCLUSION

The purposes of doing this research project are to study the co-crystal formation of ibuprofen and glutaric acid using slow cooling technique besides characterize the co-crystal that formed. In this research, it focuses on the ability of the co-former used which is glutaric acid to form co-crystal with the active pharmaceutical ingredient which is ibuprofen using slow cooling technique in the presence of 1-propanol solvent. From the result obtained, it shows that glutaric acid is able to form co-crystal with presence of 1-propanol using slow cooling technique. However, it can only perform the co-crystal if the using high ratio of glutaric acid towards ibuprofen. This is because, if using lower ratio of glutaric acid to ibuprofen, it will not formed co-crystal. As precaution step, the condition of ibuprofen-glutaric acid co-crystal is not very stable in the presence of 1-propanol. If the co-crystal is let too longer in the presence of 1-propanol, it will turn back to liquid. So, to avoid that happen, make sure that the co-crystal is dried quickly after the crystal is formed. From the result obtained by optical microscope, it can be concluded that, the co-crystal of ibuprofen-glutaric acid produce different morphology for different ratio of sample. The result that obtained from FTIR analysis also shows proof that there is hydrogen interaction that occurs between ibuprofen and glutaric acid slow cooling takes place. Lastly, based on the result obtained from the DSC, there is formation of new melting of the co-crystal as compared to their pure component. Thus, it is indicating that the sample is successfully to perform the binary nature of co-crystal. It is also shows that there is no mixture or other unwanted substances presence in the co-crystal. As a conclusion, the objective of this research project had achieved since the co-crystal formation of ibuprofen-glutaric acid using slow cooling technique in the present of 1-propanol is successfully to be produced. Thus, glutaric acid is suitable to be used as co-former for the formation of co-crystallization of ibuprofen.

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