Cocrystal Screening of Ibuprofen with Oxalic Acid and Citric Acid via Grinding Method

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Abstract. Ibuprofen is a Class II Biological Safety Class (BSC) drugs used for relief of arthritis, as an analgesic and possesses the effect of antiplatelet. The major problem involves in ibuprofen is it has a low solubility and high permeability thus causes an unsatisfactory therapeutic effect to humans. Thus, in this work, alteration of ibuprofen's physicochemical properties is conducted by means of cocrystallization technique. Co-crystallizations of ibuprofen were prepared with selected coformers using dry grinding and liquid assisted grinding (LAG) techniques in different molar ratios while ethanol and propanol were used as a solvent. The new crystalline forms were identified and characterized by differential scanning calorimetry (DSC), powder X-ray diffraction (PXRD) and fourier transform infrared spectroscopy (FTIR). Analysis for Ibuprofen-Citric acid (IBP-CA) system, co-crystal was successfully formed in 1:2, 1:3, 2:1 and 3:1 molar ratios for neat grinding method although the co-crystal produced is unstable. Meanwhile, for Ibuprofen-Oxalic acid (IBP-OA) system, the co-crystal formation was identified only in 1:1, 1:2 and 1:3 molar ratios for the neat grinding method. LAG method shows that co-crystal formation was unsuccessful in both solvents for IBP-CA, while IBP-OA co-crystal was formed in the molar ratio 1:1, 2:1 and 3:1 in ethanol, and 2:1 and 3:1 in propanol.

1. Introduction

Co-crystal is structurally homogenous crystalline materials contain two or more neutral building blocks that are present in definite stoichiometric amounts [4]. While pharmaceutical co-crystal can be defined as co-crystal with one of the co-crystal components as an API and the other components are called as co-formers or excipient [5]. In other words, it is a crystalline complex of two or more neutral molecular components tied together in the crystal lattice through interactions of the non-covalent bond, essentially hydrogen bonding [6]. The resulting multi-component crystalline phase retains the intrinsic activity of the parent API.

Ibuprofen is an active pharmaceutical ingredient (API) known as non-steroidal anti-inflammatory drug (NSAID with low solubility and high permeability thus causes an unsatisfactory therapeutic effect to humans. Alteration of the physicochemical properties of crystalline active pharmaceutical ingredients (APIs) by introducing a pharmaceutically suitable compound is a present strategy in drug formation and dosage optimization [1]. The use of co-crystallization technology in active pharmaceutical ingredient (API) crystallizations allows the technology to bring improve pharmaceutical products to the market place as well as for the improved drug delivery [2]. It has garnered much attention in the pharmaceutical industry since the formation of co-crystals can improve the properties of an active pharmaceutical ingredient (API) such as solubility, bioavailability, storage,

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stability, and manufacturability [3]. In this paper, Ibuprofen is selected as the API and the coformer used are Oxalic acid and Citric acid. Cocrystal formation between IBP and coformers are conducted using neat grinding and liquid assisted grinding method. The main objective of this paper is to explore the cocrystal formation between Ibuprofen and selected coformers as a method to improve the physicochemical properties of the model drug. Analysis of thermal and crystallinity properties of cocrystal are also examined.

2. Material and Method

2.1. Material

Ibuprofen (IBP, MW = 206.29 g/mol) was purchased from Shasun Pharmaceutical Limited, India (Batch No.: IB 11070248) (SN Grade). Citric acid (CA, MW = 192.124 g/mol), Oxalic acid (OA, MW = 90.0349 g/mol), Ethanol (MW = 46.07 g/mol) and Propanol (1-propanol, MW = 60.1 g/mol) were obtained from Sigma-Aldrich (Selangor, Malaysia). All compounds were used as received without further purification.

2.2. Method

2.2.1. Sample Preparations

The samples were prepared using neat grinding and liquid assisted grinding method. Additional three drops of solvent, Ethanol was added for the liquid assisted grinding method. Co-crystal blends of Ibuprofen-Citric acid and Ibuprofen-Oxalic acid were prepared by using oscillatory ball milling (Mixer Mill MM400, Reysch GmbH, Germany). The ball milling samples were produced by placing Ibuprofen-Citric acid and Ibuprofen-Oxalic acid at the molar ratios of 1:1, 1:2, 1:3, 2:1 and 3:1 into 25 ml milling jars with four 6 mm in diameter of stainless steel balls. Milling is carried out at 30 Hz for 30 min before it was characterized using various analytical techniques including Differential Scanning Calorimetry (DSC), X-ray Powder Diffraction (XPRD) and Fourier Transform Infrared (FTIR) Spectroscopy.

2.2.2. Differential Scanning Calorimetry (DSC)

DSC thermograms were obtained using DSC 820 (Mettler Toledo Inc., Columbus, USA) under nitrogen gas flow of 10 mL/min. Sample powders (approx. 8.5 mg) were analysed in 30 μL non-hermetic sealed aluminium pans. All samples were analysed between 25 °C and 250 °C at a heating rate of 10 °C/min and the melting point was recorded.

2.2.3. X-ray Powder Diffraction (XPRD)

XPRD was performed using x-ray diffraction analyser (Rigaku D/Max-2000, Woodlands, USA) using Cu Kα radiation (λ = 1.542 Å) in continuous scanning mode. An acceleration voltage and current of 40 kV and 30 mA were used. Data were collected over an angular range of 5o and 50o 2Θ with a scan speed of 0.5° over 2°/min.

2.2.4. Fourier Transform Infrared (FTIR) Spectroscopy

FTIR analytical method used FTIR spectrophotometer (Perkin Elmer Spectrum One, USA) that conducted the optical detection using $LiTaO_3$ detector with CsI beamsplitter that has a wavelength range of 7,800-225 cm^{-1}. For each sample, the scan is conducted in the range of 500 to 3500 cm^{-1}.

3. Result and Discussion

3.1. Thermal Analysis of Ibuprofen-Citric Acid and Ibuprofen-Oxalic Acid Co-Crystal Screening

The screening of the Ibuprofen-Citric acid (IBP-CA) and Ibuprofen-Oxalic acid (IBP-OA) formation was carried using the molar ratio 1:1, 1:2, 1:3, 2:1 and 3:1. The ground products from the experiment were analyzed using DSC. With DSC, the heat flow into and out of the sample and all the transitions or reactions due to energy changes involved can be measured [7]. Figure 1(a) shows the thermogram analysis of Ibuprofen-Citric acid (IBP-CA) sample produced using the neat grinding method. Based on

figure 1, pure Ibuprofen shows the melting peak at 75.82°C and Citric acid shows the melting peak at 151.59°C while the melting temperature of Oxalic acid is at 187-195°C. The melting points of pure substances were in good agreement with the value published in the literature [3,8,9]. There was another peak appeared from the thermogram of pure Oxalic acid at 101.14°C. This is the point where Oxalic acid shows dihydrate characteristic. This is due to an adsorption of water molecules on Oxalic acid particle [10].Figure 1 also shows that there is a possibility for the formation of co-crystal for the molar ratio of 1:2, 1:3, 2:1 and 3:1 from the presence of a peak at the beginning of the thermogram. However, peaks at the beginning of the thermogram show the unstable co-crystal formation. The peaks for the pure components are also observed where there is a slight shift in the peaks to a lower temperature, occurred as a result of interaction induced by thermal energy between the drug and the coformer during the DSC scan of the sample [11]. Meanwhile, only peaks for pure components are observed for molar ratio 1:1 indicating that the formation of co-crystal is unsuccessful. For Ibuprofen-Oxalic acid (IBP-OA) system, the possibility of co-crystal formation was identified only in 1:1, 1:2 and 1:3 molar ratios whereas only peaks for pure components are observed for molar ration 2:1 and 3:1.

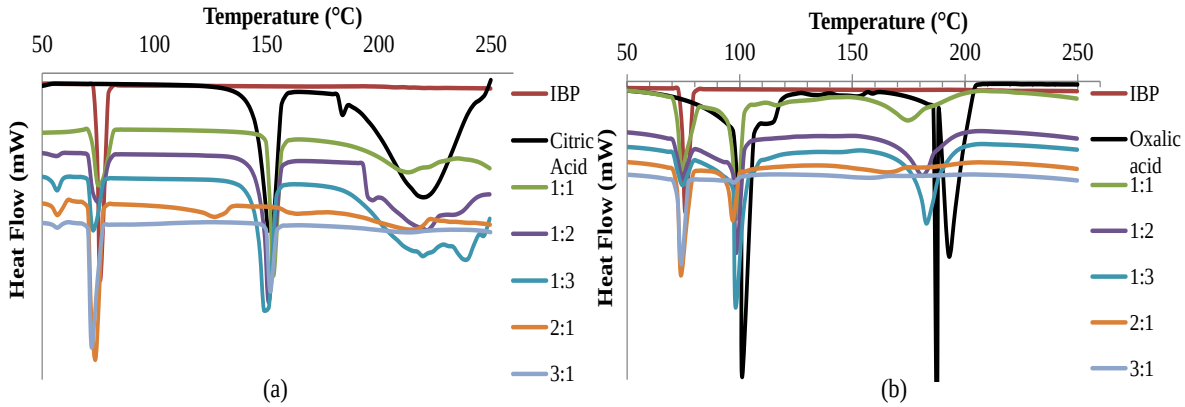


Figure 1. Differential scanning calorimetry (DSC) analysis of (a) IBP-Citric acid and (b) IBP-Oxalic acid in different molar ratio, using neat grinding method showing the possibility of the formation of co-crystal.

Figure 2(a) and (b) shows the DSC thermogram for IBP-CA and IBP-OA respectively at different ratio prepared using liquid assisted grinding method with ethanol used as the solvent. From the thermogram, there is no new peaks are observed for IBP-CA while there are new peaks observed for IBP-OA at ratio 1:1. 2:1 and 3:1. However, the peaks for pure components are also observed giving an early indication that mixtures of pure components and co-crystal exists. Grinding of IBP-CA assisted with propanol also shows no formation of cocrystal occur as shown in figure 3(a) as no new peaks are observed. Liquid assisted grinding of IBP-OA using propanol shown in figure 3(b) shows a probability for mixtures of pure components and co-crystal to exist at ratio 2:1 and 3:1 as small peaks are observed between IBP and Oxalic acid. The melting temperature of IBP-CA is slightly increase as the ratio increase as shown in figure 3(a). This indicates a significantly increase on intermolecular bonding of pure component with the present of ethanol and propanol solvent. This may potentially be the reason of unsuccessful attempt to form IBP-CA cocrystal via LAG method [12]. The IBP and the co-formers used in this work have more than one pKa values, reflecting the ionization constants of acidic and basic moieties of the molecules. According to the 'rules of three', the possibility of salt formation between drug molecule with wide array coformer candidates, their pKa differences should be more than 3 unit ($\Delta pKa > 3$). The pKa value of Ibuprofen is 4.9. Citric acid has three differences of pKa values which are 3.08, 4.74 and 5.40 while Oxalic acid is 1.23 and 4.19 [13]. Thus, there will be a various difference of pKa, (ΔpKa) between Ibuprofen-Citric Acid and Ibuprofen-Oxalic Acid. Table 1 below shows the ΔpKa values according to the type of mixtures. It shows that the differences in values of Ibuprofen-Citric Acid are less than 3. Therefore, Ibuprofen and Citric acid have a greater probability of forming cocrystal instead of salt formation. While for Ibuprofen-Oxalic Acid, one of the value

shows the greater value to form salt because of it more than 3. Thus, the mixture of Ibuprofen-Oxalic Acid can be in cocrystal form or maybe in salt form [14].

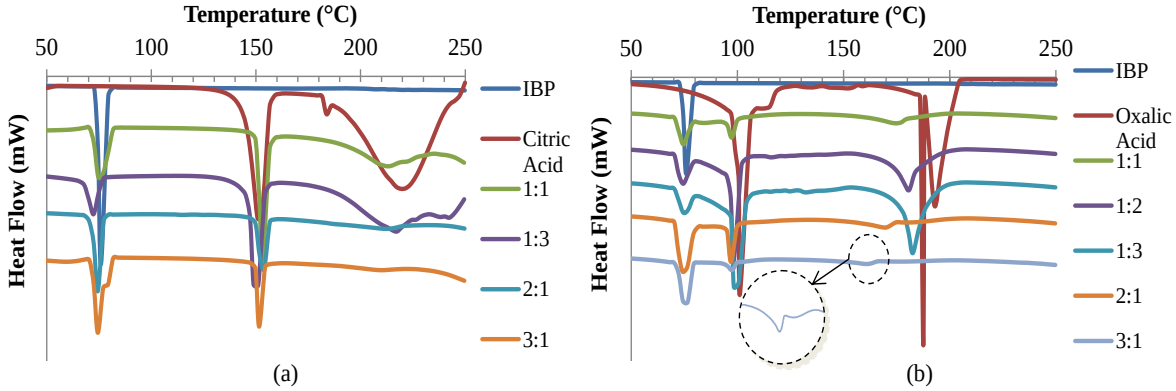


Figure 2. Differential scanning calorimetry (DSC) analysis of (a) IBP-Citric acid and (b) IBP-Oxalic acid in different molar ratio, using liquid assisted grinding method with ethanol solvent.

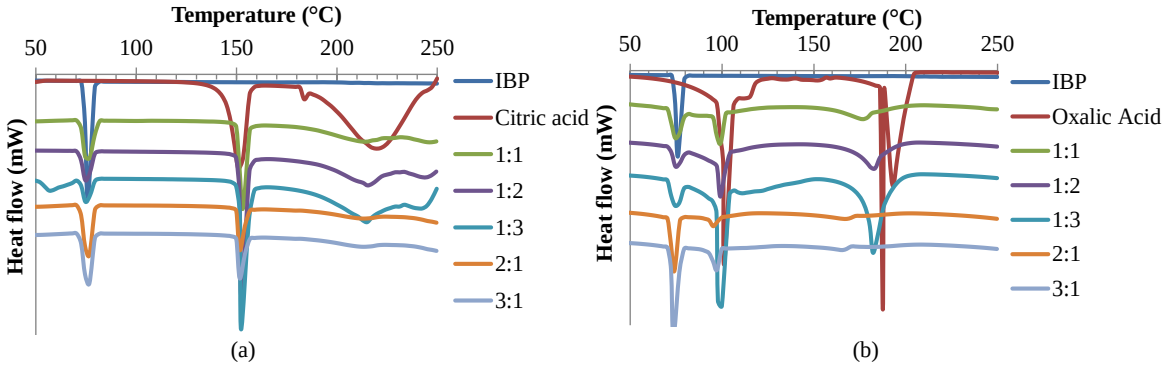


Figure 3. Differential scanning calorimetry (DSC) analysis of (a) IBP-Citric acid and (b) IBP-Oxalic acid in different molar ratio, using liquid assisted grinding method with propanol solvent.

Table 1. Difference in pKa, (ΔpKa) values of Ibuprofen-Citric Acid and Ibuprofen-Oxalic Acid

Type of Mixtures	(ΔpKa)
Ibuprofen-Citric Acid	1) 4.91 – 3.08 = 1.83 2) 4.91 – 4.74 = 0.17 3) 4.91 – 5.40 = -0.49
Ibuprofen-Oxalic Acid	1) 4.91 – 1.23 = 3.68 2) 4.91 – 4.19 = 0.72

3.2. Crytalline Phase Transformation and Proton Transfer Determination

Further investigation was conducted by characterizing the product using XPRD and FTIR to confirm the formation of co-crystal. Figure 4(a) and (b) shows the XPRD and FTIR analysis for Ibuprofen-Citric acid using the dry grinding method. The ratios between IBP and CA were varied stoichiometrically i.e. 1:1, 1:2, 1:3, 2:1 and 3:1. In figure 4(a), the XRPD data show that new peaks were detected in the ratio of 1:1, 1:3, 2:1 and 3:1. New peaks show the probability of co-crystal formation. New peaks are still detected for ratio 1:1 even if the DSC thermogram shows no new peak for melting point. No new peaks for 1:2 are observed in the XRPD profile even if there is a peak detected using DSC. The inconclusive result is obtained based on the analysis for 1:1 and 1:2 ratio.

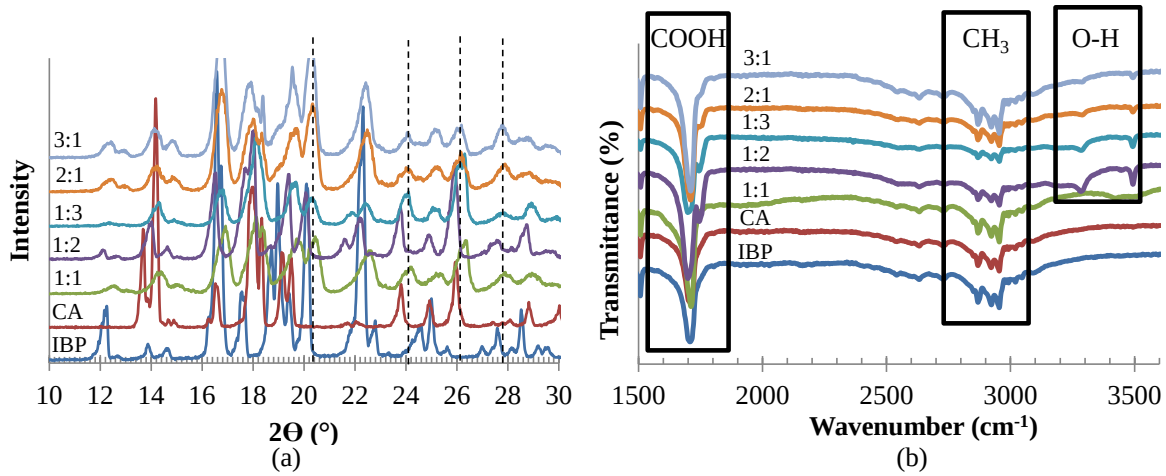


Figure 4. (a) XPRD profile and (b) FTIR spectrum for IBP-CA at different mole ratio using the dry grinding method.

Meanwhile, figure 4(b) shows the trend of FTIR spectrum for IBP-CA at varies ratio for the dry grinding method. The spectrums with band lower than 1500cm^{-1} are not shown because it is considered as the fingerprint region that is rarely diagnostically useful and rarely used to identify the functional group [15]. There are possibilities of proton transfer at both pure component (IBP and CA) as both consists of –COOH bond in the molecular structure. There are new peaks at wavenumber between 3200-3500cm^{-1} at ratio 1:2, 1:3, 2:1 and 3:1 that belongs to the O-H group. This indicates a new interaction occurs between IBP and CA at the respective ratio. Since no solvent is used in dry grinding, it can be concluded that no solvates were observed, however, the formation of salt cannot be concluded. Based on the 'rules of three', according to the ΔpKa values between IBP and CA, there is a high probability that co-crystal occurs for ratio 1:2, 1:3, 2:1 and 3:1.

As for the dry grinding method of IBP-OA, new peaks are observed for ratio 1:1, 1:2 and 1:3. This supports the preliminary result shown in DSC thermogram figure 1(b) where new melting temperatures were observed. Figure 5(a) shows the XRPD profile having at least 0.2° difference between OA and pure components for IBP-OA at ratio 1:1, 1:2 and 1:3 using the dry grinding method. There are no new peaks are observed for the ratio of 2:1 and 3:1 for IBP-OA using dry grinding. New peaks are observed for every ratio used for IBP-OA prepared using liquid assisted grinding with both ethanol and propanol solvents as depicted in figure 5(a) and (b) even though DSC only shows new peaks for ratio 1:1, 2:1 and 3:1 for ethanol and 2:1 and 3:1 for propanol. This is probably due to the phase transformation of the molecules. Meanwhile, the FTIR spectrum of 1:1, 1:2 and 1:3 IBP-OA with ethanol and ratio 2:1 and 3:1 IBP-OA with propanol follows the same trends as depicted in figure 4(b) where the functional group of COOH and CH_3 are present in the compound, with no clear indication of OH group present. Thus, the formation of salt cannot be clearly determined.

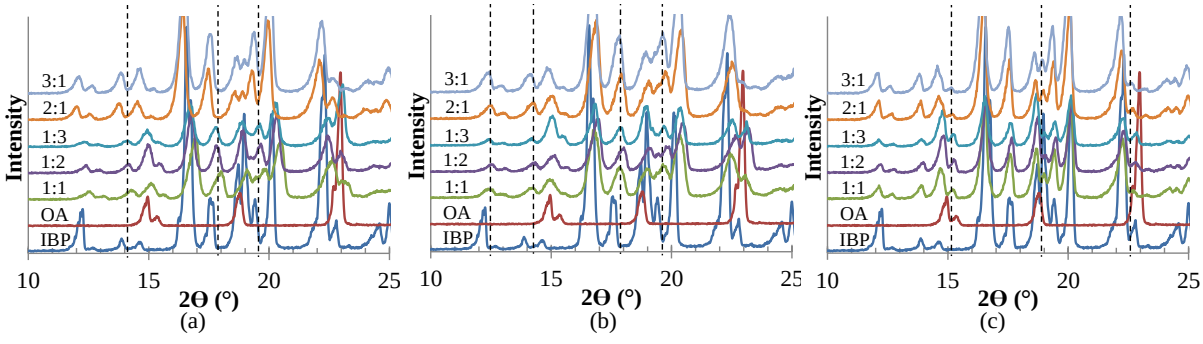


Figure 5. XPRD profile for IBP-OA using (a) dry grinding, (b) liquid assisted grinding using ethanol and (c) liquid assisted grinding using propanol at different mole ratio.

4. Conclusion

Formation of Ibuprofen-Citric acid (IBP-CA) and Ibuprofen-Oxalic acid (IBP-OXA) co-crystal was detected in the molar ratio 1:2, 1:3, 2:1 and 3:1 and 1:1, 1:2 and 1:3 respectively using the neat grinding method. Meanwhile, no IBP-CA co-crystal was formed using LAG method for both solvents. IBP-OXA co-crystal was formed in the molar ratio 1:1, 2:1 and 3:1 in ethanol, and 2:1 and 3:1 in propanol. Confirmation of co-crystal was made using XRPD analysis and FTIR spectrum determination where there is a high possiblity that co-crystal was formed for IBP-CA at ratio of 1:2, 1:3, 2:1 and 3:1, while salt formation was inconclusive for IBP-OA at ratio of 1:1, 1:2 and1:3 using neat grinding method. New peaks were determined using XRPD for IBP-OA in ethanol and propanol indicating phase transformation occurs, however, the salt formation cannot be clearly determined. For future work, solution crystallization with controlled parameters can be employed in order to assess a further details on cocrystal formation.

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