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Study on the co-crystal formation of ibuprofen and oxalic acid via evaporation method

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Abstract

Co-crystallisation 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 can enhance the physicochemical properties of the API including solubility, stability, dissolution rate, melting point and its bioavailability. Due to this, the research for the co-crystallisation of the Ibuprofen and oxalic acid as it co-former had conducted by using the slow evaporation method. The analysis and characterisation of this co-crystal was conducted by using the optical microscope, Fourier transform infrared spectroscopy (FTIR), differential scanning calorimeter (DSC), and X-ray diffraction (XRD). The observation using optical microscope had shown that the co-crystal grew in the dendrite and rod shape. From the characterisation of the co-crystals in FTIR, it shows the shift of peak which revealed the formation of the co-crystal structure. Then, the DSC showed that the melting point of co-crystals were higher than the pure ibuprofen. This showed that the co-crystal had higher thermodynamic stability than the pure API. The characterisation of the ibuprofen-oxalic acid (IBP: OA) co-crystal by using the XRD had proved that there is new crystallographic structure formed by comparing it with the pure compound. These results showed the co-crystals had formed.

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1.0 Introduction

Active pharmaceutical ingredient (API) is a substance that is active containing in the pharmaceutical products such as tablets. The dosage of API is according to their function for treatment, otherwise it also affect the diseases. This API is usually mixed with the excipients to form the pharmaceutical medicine as it cannot be present on its own because it poses low solubility and stability. Therefore, the enhancement of the API characteristics is believed can be achieved by forming the co-crystal that combines with the co-former. The co-former selection is the challenging parts in forming a co-crystal. Its need a trial and error until the co-crystal is formed. The organic acid is likely to be used as conformer in co-crystallization process, for example, the oxalic acid. Oxalic acid, $C_2H_2O_4$ is an organic compound which consists of two carboxylic acids. It is a strongest acid and acts as a reducing agent. It is also called as ethanedioic acid (Molecular weight 90.03) which usually presents in plants and vegetables.

Ibuprofen is a well-known drug in nonsteroidal anti-flammatory drug (NSAID) for relieves pain and chemically named as 2-(4-isobutylphenyl) propanoic acid (Gordon & Amin, 1984). It also used to relief the arthritis, fever and act as analgesic. The physicochemical properties of the co-crystal such as solubility, bioavailability, stability, melting point, and intrinsic dissolution are important in the development of the APIs. Ibuprofen has unique physicochemical properties as its pK_a value is 4.4–5.2. It also has an amphiphilic characteristic that leads to a 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). Ibuprofen is classified in class II of the Biopharmaceutical Classification System, has high permeability and low solubility in water (Frederico & Carneiro, 2013). Currently, it had been supplied a form of tablets, thus, the formation of the co-crystal of the ibuprofen and the oxalic acid is believed can enhance its solubility, stability, and the dissolution rate. Based on research done by Walsh et al. (2003), the co-crystal of ibuprofen with other API which is nicotinamide had been discovered to enhance its solubility by the solvent evaporation method.

Solvent evaporation is one of the methods used in

producing co-crystal. It is a type of solvent-based crystallisation technique. This technique uses a solvent to dissolve the mixture of API with conformer and then has to be evaporated until the co-crystal is formed (Mounika et al., 2015, Ali & Abolghasem, 2014). In the pharmaceutical co-crystals, the compound that has the lower solubility, then the other one will be precipitated 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 solvent. (Tanvee & Deshpande, 2014)

The objective of this paper is to study the formation of ibuprofen and glutaric acid co-crystal via slow evaporation technique in ethanol solvent. The physicochemical properties of ibuprofen and glutaric acid co-crystal are assessed through the characterization of crystal product using analytical instruments such as optical microscopy, FTIR, DSC and PXR.

2.0 Methodology

2.1 Materials

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. Ethanol (MW = 46.07 g/mol) was purchased from Sigma-Aldrich, Germany. All compounds were used without further purification.

2.2 Preparation of ibuprofen-oxalic acid

Slow evaporation technique was used in this work to produce a co-crystal (Mounika et al., 2015). Five molar 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 2.292 g of the ibuprofen mixed with 0.639 g of oxalic acid. Then, 5 ml of ethanol(solvent) was added to dissolve the ibuprofen and oxalic acid. The solution then was heated at 50 °C and increased until all the solute dissolved. These steps were repeated for four different mole ratios (1.5:1, 2.5:1, 3.5:1, and 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 Table 1. For the next experiment, the ibuprofen and oxalic acid were dissolved in the solvent ethanol. The concentrations for each molar are stated in Table 1.

Table 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

2.3 Optical microscopy analysis

The sample was taken from the solution. The morphology of the ibuprofen-oxalic acid co-crystal was observed by using optical microscope (Meiji Techno 1599) equipped with digital camera device (Model: ZC 505) and Zarbecco software for live viewing and capturing of images of the co-crystal morphology on the computer screen.

2.4 Fourier transform infra-red spectroscopy (FTIR analysis

Fourier transform infra-red spectroscopy used in this study is of Thermo Nicolet model. This instrument measures the IR spectra of the sample by using the wavenumbers in the range of 1500 to 4000 cm^{-1}. The analysis was performed to study the molecular interaction of the ibuprofen-oxalic acid co-crystal.

2.5 Differential scanning calorimetric (DSC) analysis

The harvested samples were weighed and analysed using the DSC 820 (Metler Toledo) insturment. Eight milligram of co-crystal formed was heated at heating rate of 10 °C/min. The nitrogen gas was used as the supply gas, and the process was heated from 0–400 °C. The results of the measurement was recorded.

2.6 2.6 X-ray powder diffraction (XRPD) analysis

The sample was dried in an oven at 40 °C and being crushed using portal and mortar to get the co-crystal in powder form. The sample of co-crystal formed was analysed using the powder diffractometer (Rigaku) with Cu Kα, tube voltage of 40 kV, current of 40 mA. Then, the sample was placed on a thin glass and the

patterns were being examined from 3° to 40° at 2θ values with the steps size 0.01° per minute.

3.0 Results and discussion

3.1 Co-crystal of ibuprofen-oxalic acid morphology

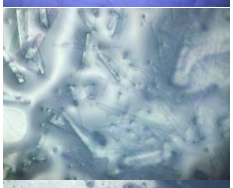
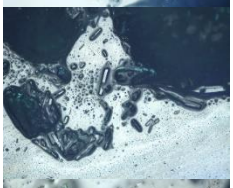
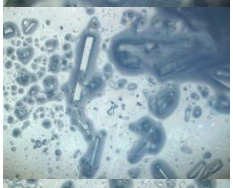
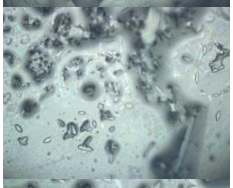
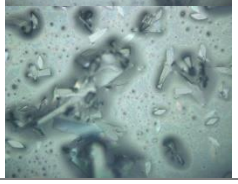
The crystals grew like a thin rod shape in the molar ratio of 0.5:1 and started to formed dendrite shape in 1.5:1 ratio with more branches as shown in Table 2. It was observed that for the 2.5:1 and above, the observations were not so clear as the crystal had broken during the preparation for the slide. There were fewer solutions left in the vials which most of them were converted into crystal form. The crystal form in the 2.5:1 seems like thin rod shape. The same shape was formed in the 3.5:1 sample. The 4.5:1 has shown the crystals like leave plate shape and the large crystal form is a rod shape. From these results, it proved that the co-crystal of ibuprofen and oxalic had formed because of the change in the structure and shape from the pure component.

3.1 Characterisation results of Ibuprofen-oxalic acid co-crystal

Fig. 1 shows the result from the FTIR analysis. The analysis had been performed for the pure ibuprofen, pure oxalic acid and co-crystal in 0.5:1, 1.5:1, 2.5:1, 3.5:1, and 4.5:1. The FTIR spectrum for the ibuprofen revealed peaks at 1506.96 cm^{-1} which was assigned as aromatic ring C=C–C, 1700.77 cm^{-1} as carboxylic acid, 2867.90 cm^{-1}, and 2954.19 cm^{-1} as methyl C–H. While for the oxalic acid, the peaks revealed at 3412.46 cm^{-1} and 1668.44 cm^{-1} represent as the hydroxy group OH and C=C, respectively.

The shift of peaks can be seen in the co-crystal 0.5:1 molar ratio as the peaks that can assigned as carboxylic acid is at 1706.46 cm^{-1}, 2.5:1 molar ratio at 1702.29 cm^{-1}, 3.5:1 molar ratio at 1704.51 cm^{-1}, and 1704.98 cm^{-1}.The new peak for the molar ratio 4.5:1 appears at 1730.95 cm^{-1} which can be assigned as ester or aldehyde functional group. However, for the ratio 1.5:1 co-crystal, the peaks of oxalic acid at 1668.44 cm^{-1} had shifted to 1677.42 cm^{-1}.

Table 2: Morphology of co-crystal of ibuprofen-oxalic acids using 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			

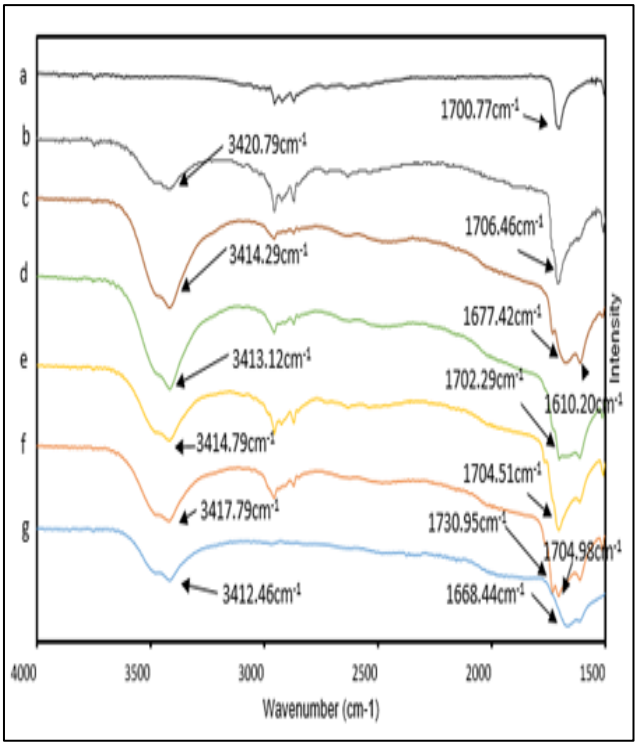


Fig.1: FTIR results for the pure IBP(a); co-crystal of 0.5:1(b), 1.5:1(c), 2.5:1(d), 3.5:1(e), 4.5:1(f) molar ratio, and pure oxalic acid(g).

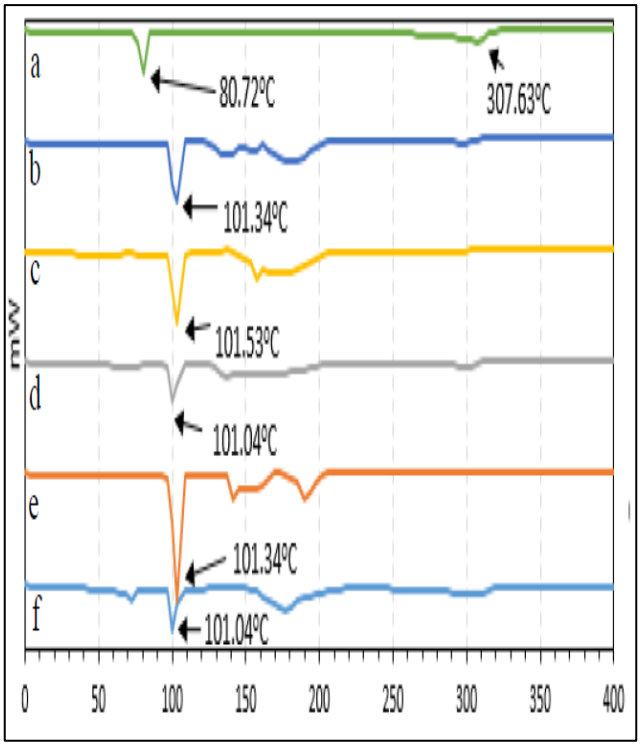


Fig. 2: DSC curves of the pure IBP (a), co-crystal of 0.5:1(b), 1.5:1(c), 2.5:1(d), 3.5:1(e), and 4.5:1(f) molar ratio.

These peaks are assigned as the C=C. The new peak at 1610.20 cm^{-1} presented in the molar ratio 1.5:1 which can be indicated as aromatic ring. Another peak was formed for the oxalic acid, which can be characterised as hydroxy group, OH which is at 3412.46 cm^{-1}. This peak had shifted to 3420.79 cm^{-1}, 3414.29 cm^{-1}, 3413.12 cm^{-1}, 3414.79 cm^{-1}, and 3417.79 cm^{-1} at molar ratio 0.5:1, 1.5:1, 2.5:1, 3.5:1, and 4.5:1, respectively.

The IR spectra peaks for co-crystals, ibuprofen and oxalic acid were summarised in Table 4. Fig. 2 represents the curves for the co-crystal of the 0.5, 1.5, 2.5, 3.5, 4.5 oxalic acid and pure ibuprofen. The peaks of 0.5:1, 1.5:1, 2.5:1, 3.5:1, and 4.5:1 co-crystals show at temperature of 101.04 °C, 101.34 °C, 101.04 °C, 101.53 °C, and 101.34 °C, respectively. While the pure ibuprofen shows a melting point peak at 80.72 °C which are endothermic signal. These showing that the co-crystals have higher thermodynamic stability than the API which is ibuprofen itself. The higher energy was needed by the co-crystals to break the crystal lattice. Some research had presented the value of peaks appear for the oxalic acid from the characterisation of the DSC was at 195.38 °C, which is higher than the co-crystal melting point (Oana et al., 2012). These can be proven that the co-crystal had formed in the molar ratio of 0.5:1, 1.5:1, 2.5:1, 3.5:1, and 4.5:1.

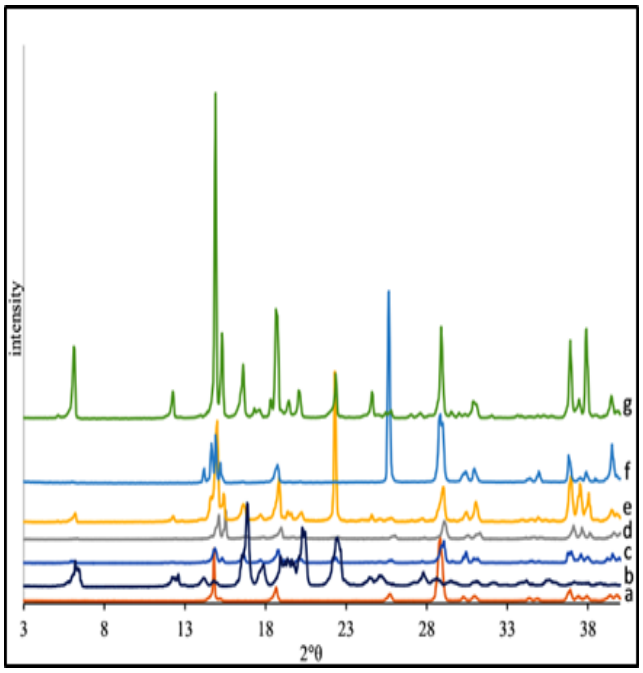


Fig. 3: XRD results for the pure oxalic acid(a), pure IBP(b), co-crystal of 4.5:1(c), 3.5:1(d), 2.5:1(e), 1.5:1(f), and 0.5:1(g) molar ratio.

However, there are also another small peak appear after that. The instability of the co-crystal structure had observed due to the formation of another peak in the all those co-crystals. These peaks indicate that there is instability is form in that temperature. For example, ibuprofen showing one more peak at temperature 307.6 °C, therefore, the crystallinity of the ibuprofen

was broken in that temperature. The peaks can be summarised in the Table 3.

While in Fig. 3, it presents the diffractogram of the co-crystals and it pure compounds which were ibuprofen and oxalic acid. The diffractogram of the ibuprofen can be observed the peaks at 2θ: 12.26°, 24.54° and 37.66°. Meanwhile peak observed for oxalic acid are 14.80°, 18.66°, 25.72°, and both pure compounds show a good agreement with the value published in the literature (Jang et al., 2017).

Table 3: The temperature of other peaks formed at each co-crystals and pure ibuprofen**.**

Molar ratio	Temperature (°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 4: IR spectra peaks for co-crystals, 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	-

4.0 Conclusion

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

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