Study on Co-Crystal Formation of Ibuprofen and Oxalic Acid Via Slow Cooling Technique

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***Abstract*— Pharmaceutical co-crystals can improve the solubility, physicochemical properties as well as their chemical properties. In this study, the interaction between Active Pharmaceutical Ingredients (API) Ibuprofen and the conformer, oxalic acid to crystallize into a newly formed drug is experimented viz slow cooling method. The cooling rate is set to 0.5°C/min. The co-crystal obtained is analysed by using PXRD, FTIR, DSC and optical microscopy.**

Keywords*— ibuprofen; oxalic acid; cocrystals; slow cooling; optical microscopy; DSC; FTIR; XRD; physicochemical properties; physical characterization

INTRODUCTION

In the pharmaceutical industry, less than 1% of active pharmaceutical ingredients (API) are in the market because of its poor biopharmaceutical properties, as compared to its toxicity or its inefficiency (Aakeroy et al., 2007). The main issue which relates the biopharmaceutical properties is the solubility and it had been one of the challenges the pharmaceutical industry has to overcome (Blagden et al., 2007; Qiao et al., 2011). The major issue in the biopharmaceutical industries involving API is the dissolution rates. The existing drugs available nowadays are reported to have solubility issues Hence, various methods have been used to manipulate the solid state of pharmaceutical materials on specific drug formulation problems. Among the techniques used in the pharmaceutical industry to improve the solubility and stability of problematic drugs is by crystallization, either into salts and hydrates (Chow et al., 2012). These days, there are a few drugs that have been studied like carbamazepine, itraconazole, piroxicam, norfloxacin, fluoxetin, caffein and others (Zhang et al., 2015). Since each of the APIs studied are different in its molecular structure and component, different results are expected. Co-crystals, as defined by Aakeröy and Salmon (2005) is structurally homogeneous crystalline materials containing two or more components present in definite stoichiometric amounts. Another definition of pharmaceutical co-crystal is a co-crystal which its constituent element is made up of as an Active Pharmaceutical Ingredient (API) and the coformers (Aakeroy et al., 2005)

Before any co-crystals are produced physically, the formation on the co-crystals is predicted. The Cambridge Structural Database (CSD) is used for the analysis on the existing crystals, which acts as the first step in co-crystal predictions. Technically, the CSD facilitates statistical analysis of packing motifs and thereby provides empirical information concerning similar functional groups and how they interact in molecular association, that is, which explains the supramolecular synthons formation (Vishweshar et al., 2005). Another explanation on co-crystal packing motifs as explained by Desiraju (1995), supramolecular synthons are the structural units within supramolecules in which synthetic operations can form or create by manipulating its intermolecular interactions. Hence, co-crystallization method to improve its bio-availabilities and other properties has been pursued to increase its quality. Other than that, since there is no literature available for Ibuprofen-Oxalic acid co-crystal yet, hence this experiment is conducted to provide data for future uses.

METHODOLOGY

Materials

Ibuprofen (IBP) and oxalic acid (OXA) were purchased from Sigma-Aldrich Chemical Company. The raw materials are used without further purification. Solvents used are propanol and ethanol.

Preparation of OXA-IBP Cocrystals by Slow Cooling Technique

Co-crystal samples were prepared by using 2.5-4.5 mol ratio with the step size of 0.5 via slow cooling technique. Ibuprofen and oxalic acid are weighed according to the calculated ratio. The calculated amounts of Ibuprofen and Oxalic acid are added into the vials, 5mL solvents (ethanol and propanol for respective experiment) are added into each vial. The suspension is heated

to 60°C to dissolve all solids in an orbital shaker connected to a water bath. Once clear solution is formed and the no traces of precipitate, the cooling process takes place by dropping the temperature to 20°C. The cooling rate is set to 0.5°C/min.

Table 1. The amount of OXA in 5mL propanol.

Molar ratio (IBP:OXA)	Amount of IBP (g)	Amount of OXA (g)
1:2.5	2.27	2.48
1:3.0	2.27	2.97
1:3.5	2.27	3.47
1:4.0	2.27	3.96
1:4.5	2.27	4.46

Table 2. The amount of OXA in 5mL ethanol.

Molar ratio (IBP:OXA)	Amount of IBP (g)	Amount of OXA (g)
1:2.5	2.93	3.19
1:3.0	2.93	3.83
1:3.5	2.93	4.47
1:4.0	2.93	5.11
1:4.5	2.93	5.75

Investigation on The Morphology of CoCrystal

The analysis on the morphology of the co-crystallization between Ibuprofen and Oxalic acid is done via optical microscopy using Meiji Techno 1559 which is equipped with Zabecco software. The co-crystals formed in the vial is withdrawn and the morphology is observed.

Comparison of Attenuated Total Reflectance-Fourier-Transform Infrared Spectroscopy (ATR-FTIR) Investigation

The infrared spectra of cocrystals formed are investigated using with ATR-FTIR. The range of wavenumbers used for this study is from 500 to 4000 cm^{-1}. The cocrystal from the vial are filtered from the solvent in a filter paper. After the solvent had been completely evaporated, the different precipitates were vacuum dried for 24 h and stored at room temperature for DSC and XRD analysis. The dried cocrystals are then crushed to form into powder state.

Differential Scanning Calorimetry Investigations

The DSC used for thermal analysis of IBP-OXA cocrystal is performed on DSC 820 (Mettler Toledo). Approximately 2 mg of cocrystal samples are heated at rate of 10°C/min in a steam of nitrogen gas. The temperature range is set from 0°C to 400°C.

Powder X-ray Diffraction (PXRD) Investigations

PXRD patterns are collected on a powder diffractometer (Rigaku) with a Cu Kα, tube voltage of 40 kV, current of 40 Ma. The samples are placed on a thin glass. PXRD is set up by computer software. For analysis, the cocrystals are examined and patterns are recorded from 3° to 40° at 2θ values with steps of 0.01°/min

RESULTS AND DISCUSSION

The effects of different mol ratio on cocrystal morphology

The morphology of the cocrystal is observed to be a long and plate-like shape. The difference of mol ratio in both solvents results in different sizes of cocrystal. As can be seen in Fig.1 and Fig. 2, single crystals from each mol ratio are observed. The magnification set for the microscopy is 10x. The size of the cocrystal in solvent propanol is bigger than the cocrystals in ethanol.

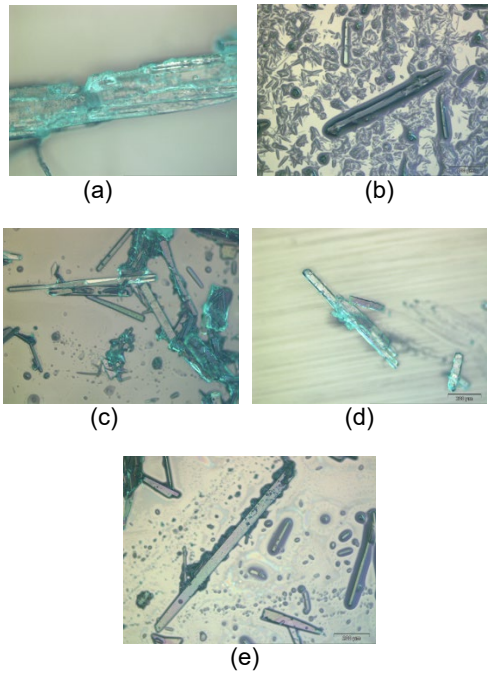


Fig. 1: The morphology of IBP-OXA cocrystal in 5mL ethanol in mol ratio of (a) 1:2.5 mol (b) 1:3.0 mol (c) 1:3.5 mol (d) 1:4.0 mol (e) 1:4.5 mol.

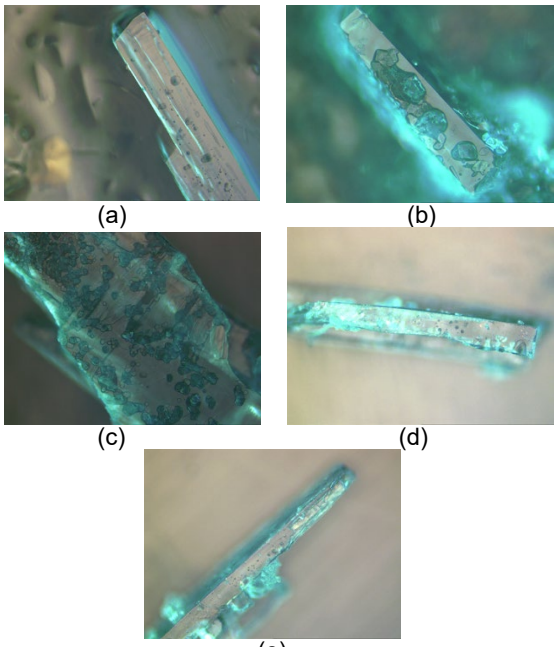
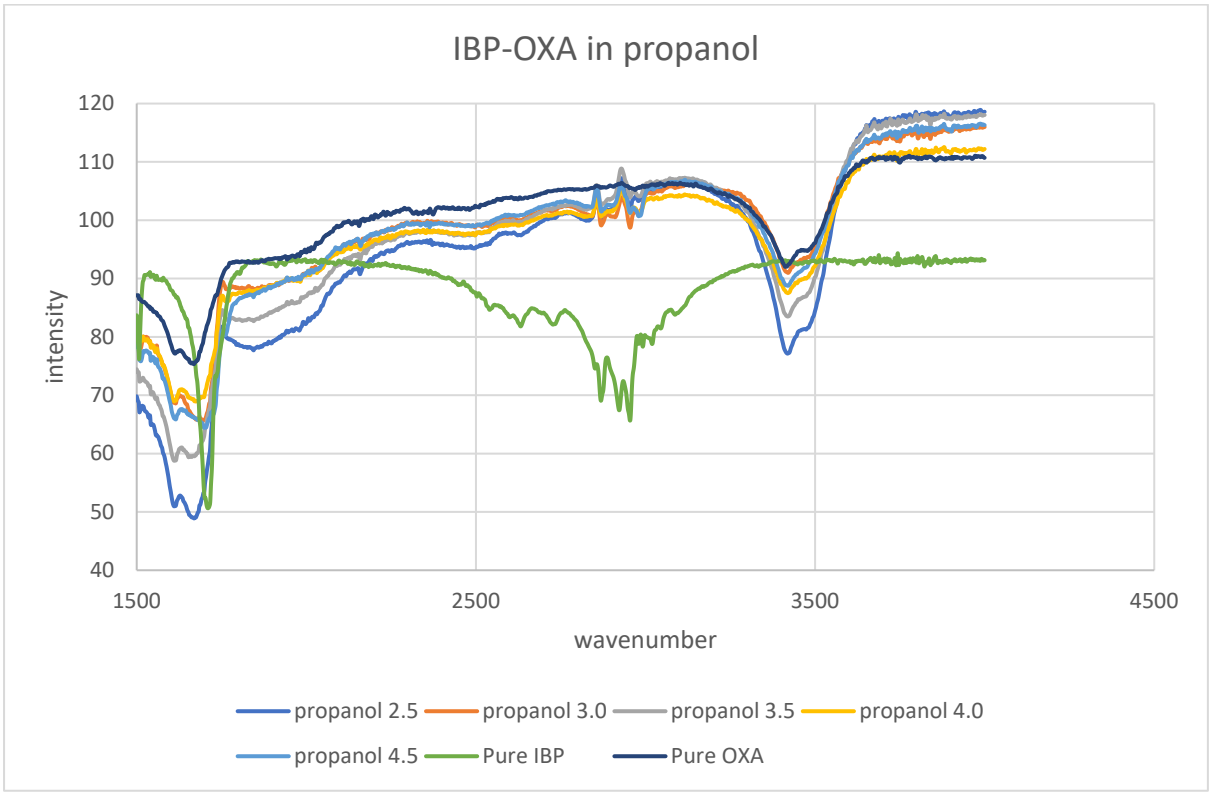
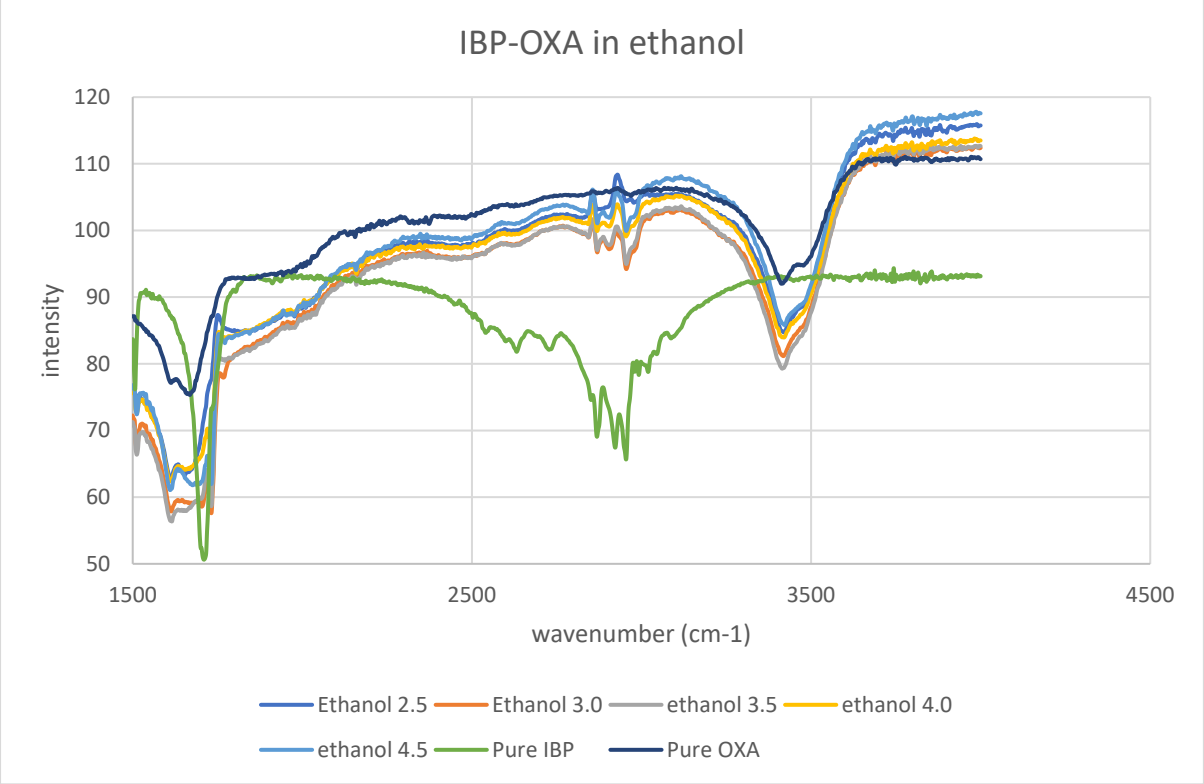


Fig 2. The morphology of IBP-OXA cocrystal in 5mL ethanol in mol ratio of (a) 1:2.5 mol (b) 1:3.0 mol (c) 1:3.5 mol (d) 1:4.0 mol (e) 1:4.5 mol.

Infrared spectroscopy study



(a)



(b)

Fig 3. The IR spectra of cocrystal in (a) ethanol and (b) propanol.

As can be seen from the FTIR spectra in Fig.3 (a), there are peaks at 3419.20cm^{-1}, 2868.81cm^{-1}, 1822.47cm^{-1} and 1614.93cm^{-1}. On the other note, in Fig. 3 (b), there are also similar peaks at 3418.91cm^{-1}, 2459.59cm^{-1}, 2869.74cm^{-1}, 1844.28cm^{-1} and 1669.19cm^{-1}. For both graphs, it can be seen that the pure IBP has slightly different peaks than the cocrystal peaks. At wavenumber 3000cm^{-1}, it represents the peak for pure IBP whish exists in both graphs. At wavenumber 3415cm^{-1} to 3420cm^{-1}, new peak has formed which indicates that a cocrystal is formed in both solvents. It can be concluded that the traces cocrystal of IBP-OXA is confirmed throughout the whole analysis.

CONCLUSION

The cocrystal formation of IBP-OXA is achievable with the method of slow cooling with rate 0.5°C/min. The properties of the cocrystal can be analysed using FTIR to detect new peaks and the attraction forces between molecules. Broad bands and new peaks are formed during the experiment. Other than that, the morphological properties of cocrystal is also analysed using the optical microscopy. This research verify that cocrystallization can improve the properties of the API and further research is helpful in the biomedical application.

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