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Carbamazepine Co-crystal Screening with Dicarboxylic Acids Co-Crystal Formers

Syarifah Abd Rahim, Fatinah Ab Rahman, Engku N. E. M. Nasir, Noor A. Ramle

***Abstract*—**Co-crystal is believed to improve the solubility and dissolution rates and thus, enhanced the bioavailability of poor water soluble drugs particularly during the oral route of administration. With the existing of poorly soluble drugs in pharmaceutical industry, the screening of co-crystal formation using carbamazepine (CBZ) as a model drug compound with dicarboxylic acids co-crystal formers (CCF) namely fumaric (FA) and succinic (SA) acids in ethanol has been studied. The co-crystal formations were studied by varying the mol ratio values of CCF to CBZ to access the effect of CCF concentration on the formation of the co-crystal. Solvent evaporation, slurry and cooling crystallization which representing the solution based method co-crystal screening were used. Based on the differential scanning calorimetry (DSC) analysis, the melting point of CBZ-SA in different ratio was in the range between 188^{o}C-189^{o}C. For CBZ-FA form A and CBZ-FA form B the melting point in different ratio were in the range of 174^{o}C-175^{o}C and 185^{o}C-186^{o}C respectively. The product crystal from the screening was also characterized using X-ray powder diffraction (XRPD). The XRPD pattern profile analysis has shown that the CBZ co-crystals with FA and SA were successfully formed for all ratios studied. The findings revealed that CBZ-FA co-crystal were formed in two different polymorphs. It was found that CBZ-FA form A and form B were formed from evaporation and slurry crystallization methods respectively. On the other hand, in cooling crystallization method, CBZ-FA form A was formed at lower mol ratio of CCF to CBZ and vice versa. This study disclosed that different methods and mol ratios during the co-crystal screening can affect the outcome of co-crystal produced such as polymorphic forms of co-crystal and thereof. Thus, it was suggested that careful attentions is needed during the screening since the co-crystal formation is currently one of the promising approach to be considered in research and development for pharmaceutical industry to improve the poorly soluble drugs.

***Keywords*—**Carbamazepine, co-crystal, co-crystal former, dicarboxylic acid.

I. Introduction

DRUG molecules with limited aqueous solubility are the common issue in the research and development portfolios of discovery focused pharmaceutical companies [1]. Pharmaceutical development will be challenging as the issue of poor solubility of drug molecule may possibly cause to slow dissolution in biological fluids, insufficient and inconsistent systemic exposure and consequent lack efficacy in patients, particularly when delivered through the oral route of administration [1]. In the pharmaceutical industry, it is the poor biopharmaceutical properties rather than toxicity or lack of efficacy that are the main reasons why less than 1% of active pharmaceutical compounds sometime produce into the marketplace [2]. Among these biopharmaceutical properties, solubility remains a key [1], with drugs often damaged during commercial production due to their low solubility.

Currently, one of the main challenges for the pharmaceutical industry is to improve the solubility of drug. The improvement of solubility and dissolution profiles of these drug molecules without changing the molecular structure is a special challenge for the successful development of pharmaceutical products [3]. Since a long time ago, there is the interest in the design of pharmaceutical co-crystals, which becomes as a potential method for improving the bioavailability of drugs with low aqueous solubility [4]. The improvements in the pharmaceutical sciences have provided several ways for solving the issues of low aqueous solubility [1]. Although some techniques are effective in order to improve the oral bioavailability, the successes of the ways are dependent at times on the specific physicochemical nature of the molecules being studied [1]. Therefore, a pharmaceutical co-crystal can be designed with the aims to improve the solid-state properties of an API without influence its natural structure [4]. A solution based method is carried out in order to determine the possibility of the formation of co-crystals from two components.

II. Materials and Methods

A. Chemicals

The CBZ, SA and FA were purchased from Sigma-Aldrich. The absolute ethanol was supplied by Fisher Scientific. All the chemicals used were with purity exceeding 99%.

B. Experimental

The experimental work was conducted using solution based approach via solvent evaporation, slurry crystallization and cooling crystallization methods [5]. Different mol ratios of CCF (SA and FA) to CBZ were prepared each with the interval of 0.25 started from 1.0 to 3.0. All the resulting solids from each method were separated using vacuum filter at room temperature. The solid produced from the experimental work were characterized using differential scanning calorimetry (DSC), x-ray powder diffraction (XRPD) and optical microscopy.

C. Solvent Evaporation

A mixture of CBZ with CCF with pre-defined mol ratios was dissolved in ethanol using an orbital shaker at a room

S. Abd Rahim is with the Universiti Malaysia Pahang, Pahang, 26300 Malaysia (corresponding author to provide phone: 609-549-2886; fax: 609-549-2889; e-mail: syarifah@ump.edu.my).

F. Ab Rahman, E. N. E. M. Nasir, and N. A. Ramle are with the Universiti Malaysia Pahang, Pahang, 26300 Malaysia (e-mail: fatinah_abrahman@yahoo.com.my, enadia_emnasir@yahoo.com ashilaramle@gmail.com).

temperature. Once the solute had fully dissolved, the solution was filtered using 0.22 μm syringe filter to remove any impurities. The filtered solution was filled in the 20 ml vial and covered with parafilm, with a few holes poked in and left to evaporate at room temperature.

D.Slurry Crystallization

A mixture of CBZ with CCF with pre-defined mol ratios was slurried in 10 ml of ethanol for 72 hours of equilibration time at room temperature in the shaker.

E. Cooling Crystallization

A mixture of CBZ with CCF in 10 ml of ethanol with pre-defined mol ratios was heated to 60°C for 1 hour in the shaker. Once the solute had fully dissolved, the solution was then cooled down at 5°C for every 1 hour interval until room temperature to induce the precipitation.

F. Crystal Characterization

Differential scanning calorimetry (DSC) was used to determine the melting point of the co-crystal produced. A mortar and pestle was used to ground the sample crystal in order to get a small size of sample for a better and more uniform thermal contact with the crucible pan. 2 to 3 mg of sample was crimped in aluminium pan and analysed in the DSC from 30 to 220°C (CBZ-SA) and 30 to 300°C (CBZ-FA), with a flow rate of 50 ml/min of nitrogen gas purging at a heating rate of 10 °C/min.

The x-ray powder diffraction (XRPD) pattern profile of the produced crystal was identified using RIGAKU (Miniflex II) diffractometer with Cu Kα radiation. The system was operated at 30 kV and 15 mA with the 2θ (angle) from 3° to 40°. The step size and step time were 0.01° and 1 second/step, respectively. In addition, the morphology of the crystal was characterized using Dino-eye microscope eye-piece and Carl Zeiss model microscope.

III. Result and Discussion

A. Differential Scanning Calorimetry (DSC)

The melting point for CBZ as shown in Table I was in good agreement with the literature which is 191°C [6] and in the range between 190°C-191°C [7]. For FA pure component, the measured melting point was detected at 293°C which in the temperature range between 287°C-302°C as reported in literature [8]. The melting point for SA which is 187°C is near the reported by previous study [9]. From the analysis, the melting point of CBZ-SA was in the range between 188°C-189°C as similar to reported study [10], [11]. CBZ-FA form A was found to be a hydrate co-crystal as proven by DSC which showing a melting between 118°C-125°C representing the existing of water followed by melting of the co-crystal at a range of 174°C-175°C [10].

B. X-ray Powder Diffraction (XRPD)

Fig. 1 shows a peak profile for the starting materials used in this study i.e. CBZ, FA and SA. The CBZ used in this research was CBZ form III confirmed by previously reported pattern profile [12]. In addition, the CCFs (SA and α form FA) pattern profiles were also been identified similar to previously reported [9] and [13] respectively.

TABLE I
DSC Analysis Results

Components	Melting Point (°C)
CBZ	191
FA	293
SA	187
CBZ-FA form A	118–125
	174-175
CBZ-FA form B	185-186
CBZ-SA	188-189

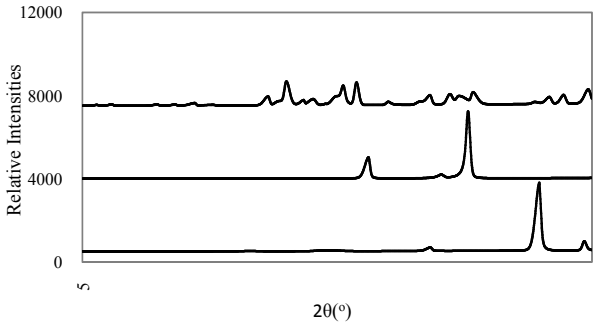


Fig. 1 XRPD profile for pure components (CBZ, FA and SA)

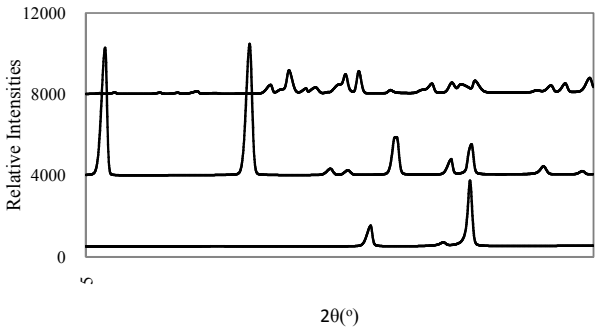


Fig. 2 XRPD profile for CBZ, CBZ-SA and SA

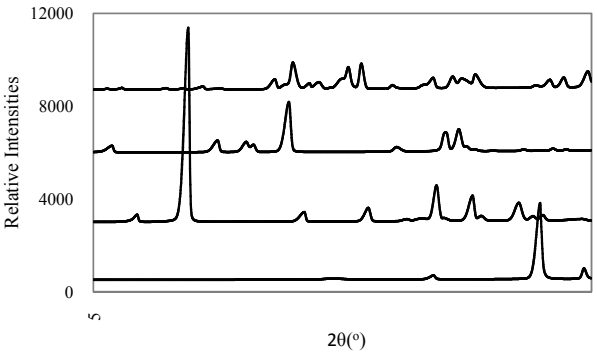


Fig. 3 XRPD profile for CBZ, CBZ-FA form A, CBZ-FA form B and FA

Figs. 2 and 3 show an example of the PXRD pattern profile for CBZ-SA and CBZ-FA obtained from the screening method respectively. Data analysis from the PXRD pattern profiles obtained has shown that the co-crystal was successfully formed as summarized in Table II.

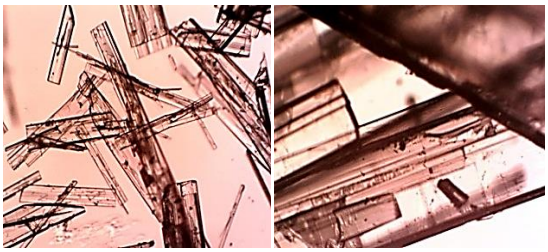
TABLE II
SUMMARY OF THE SCREENING

Mol ratio FA/CBZ	Condition	CBZ-FA form A	CBZ-FA form B	CBZ-SA
1.00	Slurry crystallization		✓	✓
1.25			✓	✓
1.50			✓	✓
1.75			✓	✓
2.00			✓	✓
2.25			✓	✓
2.50			✓	✓
2.75			✓	✓
3.00			✓	✓
1.00	Cooling crystallization	✓		✓
1.25		✓		✓
1.50		✓		✓
1.75			✓	✓
2.00			✓	✓
2.25			✓	✓
2.50			✓	✓
2.75			✓	✓
3.00			✓	✓
1.00	Solvent evaporation	✓		✓
1.25		✓		✓
1.50		✓		✓
1.75		✓		✓
2.00		✓		✓
2.25		✓		✓
2.50		✓		✓
2.75		✓		✓
3.00		✓		✓

The findings revealed that CBZ-FA co-crystal has formed into two different polymorphic forms depending on the crystallization method and the ratio of FA to CBZ. On the other hand, the CBZ-SA has only one polymorphic form. The CBZ-FA form A was found to be formed for all range of ratios studied via solvent evaporation method and at ratios FA to CBZ below 1.5 in cooling crystallization method, whereas, CBZ-FA form B was found to be formed for all range of ratios studied via slurry crystallization method and at ratios FA to CBZ above 1.5 in cooling crystallization method. The impact from the movement of the particle in the slurry during shaking and concentration of the FA in the solution are believed to have an effect on the formation of different co-crystal polymorphs [14]. Previously, the CBZ-FA co-crystal Form A and Form B was reported to be formed from saturated aqueous and near saturated or saturated ethanolic solution respectively [10].

C. Morphology

Fig. 4 shows the needle-like morphology of CBZ-FA and CBZ-SA co-crystals similar to previously reported [15]. The findings revealed no significant differences between CBZ-FA form A and form B as both have needle-like morphology. The size of the co-crystal formed by solvent evaporation was bigger as compared to cooling and slurry crystallizations. This is due to the solvent crystallization method does not involve movement of the solution (stirring or shaking) during the growing process lead to the co-crystal growth slowly. The stirring or shaking process may induce the nucleation and a lot of small crystals grow resulted the co-crystal size become smaller.



(a) (b)

Fig. 4 Crystal morphology taken at magnification of 5x for(a) CBZ-SA from cooling crystallization at ratio 2.75 and (b) CBZ-FA from solvent evaporation at ratio 1.50

IV. CONCLUSION

The findings suggested that it is crucial to conduct a multiple methods or approaches during co-crystal screening rather than reliance to only one method which may lead to inadequate in determination of the co-crystal form. This has been proven from the CBZ-FA co-crystal screening in which different methods and ratio (concentration) has an effect on the polymorphic transformation. This work also could be expanded in different solvents in order to find out the possibility of co-crystal formation or any polymorphic behaviour due to changes of the solvent in the system.

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