

# Carbamazepine-Fumaric Acid and Carbamazepine-Succinic Acid Co-crystal Screening Using Solution Based Method

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**Abstract**—Co-crystal plays a critical role in the pharmaceutical industry and becoming as an alternative approach to improve the bioavailability of poor water soluble drugs especially for a weakly ionisable groups or neutral compounds. In this study the co-crystal screening was carried out for carbamazepine (CBZ) and co-crystal former (CCF) of fumaric acid (FUM) and succinic acid (SA) using non-stoichiometric method (addition of CBZ to CCF saturated solution) and stoichiometric method (evaporation of 1:1 molar ratio of CBZ to CCF) in acetonitrile, ethyl acetate, propanol, ethanol and formic acid solvent systems. The crystals produced from the screening were characterized using Powder X-ray Diffraction (PXRD), Differential Scanning Calorimetry (DSC) and Fourier Transform Infrared (FT-IR). The PXRD analysis had confirmed that the co-crystal was successfully formed in both methods for all of the solvent system studied with an exception to formic acid in the stoichiometric method for CBZ-FUM system and in all methods for CBZ-SA system. The findings from this analysis revealed that Form A and Form B of CBZ-FUM co-crystal had been successfully formed from different solvents systems. DSC analysis had shown that the melting point of CBZ-FUM and CBZ-SA co-crystals were in the range similar to the previous study. The characterization using FT-IR indicated that the functional groups which include amides and carboxylic acids were presented in the co-crystal produced. Further study on the co-crystal solubility and dissolution rate is needed in order to access the efficacy of the co-crystal since the screening methods have been successfully confirmed the formation of the co-crystal.

**Index Terms**—Carbamazepine, co-crystal, stoichiometry, non-stoichiometry.

## I. INTRODUCTION

Co-crystallisation allows binding two or more crystal component in single crystalline lattice without breaking or making new covalent bonds [1], [2]. Co-crystals can be defined as “a stoichiometric multi-component system which connected by non-covalent interactions and present in solid form under ambient conditions”. Pharmaceutical co-crystal is a co-crystal in which at least one of the molecular components is an API and along with the other components called

co-crystal formers [3]. The role of co-crystal former help the active drug to disintegrate into small particles to be transported to the blood stream to where the drug is intended to play its role and still protect the product's stability so it will be at greatest benefits and effectiveness [4]. Co-crystals are considering as a major class of pharmaceutical materials to promote the solubility and dissolution. Apart from co-crystals, other materials such as polymorphs, salts, and amorphous solids are also widely used to enhance dissolution and bioavailability of less soluble API [5], [6].

The enhancement of drug solubility is required in the pharmaceutical industry [7]. Solubility is known as the key factors in determining the efficacy as well as the activity of a drug. Nowadays, all of the generic drug manufacturers are competing in the increasingly sophisticated market. The improvement of the drug solubility will dramatically draw their attention as this can make profit towards their business [8]. Hence, the crystal form of APIs is selected to fulfill the requirement. The improvement of the solubility can maximize the bioavailability because poor solubility in water correlates with the poor bioavailability.

Carbamazepine (CBZ) is practically insoluble in water and facing challenges of dissolution-limited bioavailability [3], [9]-[13]. CBZ is a drug that used as anticonvulsant for treatment of epilepsy and trigeminal neuralgia [14]. CBZ can be classified in class 2 drugs under biopharmaceutics classification system (BCS) [15]. Drugs in this class are analyzed to have low solubility in an aqueous media, but having a high permeability via human intestinal membrane [15], [16]. Moreover, CBZ has four different anhydrous polymorph forms and dehydrate forms, and CBZ form III is known as the mainly stable anhydrous form at ambient conditions [17]. Previous study has reported that co-crystals have been successfully formed using slow evaporation, reaction co-crystallisation, solid state grinding and slurry [18]-[23].

Hence, the aim of this study is to investigate the CBZ-FUM and CBZ-SA co-crystal formation using non-stoichiometric method which including continuous shaking and stirring and stoichiometric method of solvent evaporation in different solvent systems (acetonitrile, ethyl acetate, propanol, ethanol and formic acid).

## II. PROCEDURE

### A. Materials

The CBZ and CCF (FUM and SA) were purchased from

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ECA International Corporation and Sigma-Adrich Company respectively. Whereas, the solvents (acetone, propanol, ethyl acetate, formic acid, acetonitrile and absolute ethanol) were supplied by Fisher Scientific with purity exceeding 99%.

### B. Non-stoichiometric Crystallisation

CBZ solid was added to saturated CCF solution prepared using propanol, ethanol, acetonitrile, ethyl acetate and formic acid in 100 mL conical flask after equilibrating for 72 hours each at room temperature. The added CBZ solutions were left again to equilibrate for about 72 hours in two conditions i.e. in an automated shaker with 150 rpm at room temperature and stirred using a magnetic stirrer. The precipitate crystal was filtered using vacuum filter and dried at room temperature. All experiments were performed in triplicate.

### C. Stoichiometric Crystallisation

Stoichiometric method is carried out using solvent evaporation method with 1:1 (CBZ:CCF) molar ratio in 25 mL of propanol, ethanol, acetonitrile, ethyl acetate and formic acid. The mixture was mixed at room temperature. More solvent was added until the solutes were fully dissolved in any cases where the complete dissolution was not obtained. Once the solute had fully dissolved, another 10 mL of solvent was added into the final solution before filtered using 0.22 $\mu$ m using syringe filter and withdrawn to 20 mL vial. The solution is then covered with parafilm (with few holes) and left to evaporate at room temperature. The precipitate crystal formed was filtered using vacuum filter and dried at 30 $^{\circ}$ C for 24 hours. All experiments were performed in triplicate.

### D. Powder X-ray Diffraction (PXRD)

PXRD was used to determine the presence of co-crystal in the samples by showing different peak profiles. A RIGAKU (Miniflex II) diffractometer was operated at the operating conditions as following: (Cu K $\alpha$  radiation, voltage 30kV, current 15mA, step size 0.01, step time 1 s and angular range between 3 $^{\circ}$  and 40 $^{\circ}$  at 2 $\theta$  scales.

### E. Differential Scanning Calorimetry (DSC)

DSC model G1000 with series no. of Q1000-0567 was used to determine the melting point of the co-crystal. The samples (1-3 mg) were crimped in aluminium pans and lid then heated from 30 to 300 $^{\circ}$ C, under nitrogen purge with flowrate of 50 ml/min at a heating rate of 10 $^{\circ}$ C/min.

### F. Fourier Transform Infrared (FT-IR)

The samples were analysed by FTIR to determine the presence of certain functional groups in a molecule. The analysis was performed using FT-IR with 50 series model attached with the diamond detector at the wave number from 4000-600  $\text{cm}^{-1}$  using 32 scans per spectrum with a resolution 4  $\text{cm}^{-1}$  for each sample.

## III. RESULT AND DISCUSSION

### A. Powder X-ray Diffraction (PXRD)

The presence of co-crystal can be identified using PXRD since every crystalline solid phase has its unique PXRD pattern [24]. PXRD pattern profiles produced for all

components of CBZ, CCF (FUM and SA) and its co-crystal (CBZ-FUM and CBZ-SA) were compared to ensure that the co-crystal produced does not contain any mixture of either pure component of CBZ or CCF. As shown in Fig. 1, the pure components used in this study were CBZ Form III [17],  $\alpha$  polymorph of FUM [25] and  $\beta$  polymorph of SA [26].

From the analysis obtained, it was found that CBZ-FUM co-crystal had been successfully formed in stoichiometric and non-stoichiometric methods for all solvents used except for formic acid in stoichiometric method where no crystal was precipitated.

The results pointed that CBZ-FUM has two polymorphic forms i.e. Form A and Form B depending on the type of solvents and methods used. This finding compatible with previous, stated that method used in crystallisation process affect the polymorphic forms of co-crystal produced [23], [27]. CBZ-FUM Form A and Form B was formed from saturated aqueous and near saturated or saturated ethanolic solution respectively [28]. Mole ratios also play a role in determining the polymorphic forms of co-crystal [29]. The pattern profiles for all methods in acetonitrile and ethyl acetate show that the co-crystal possessed Form A. Differ with the usage of formic acid solvent, the co-crystal produced only in non-stoichiometric method was Form B. Different results were obtained in ethanol and propanol. The pattern profile for CBZ-FUM Form A and Form B was resulted in ethanol from stoichiometric method (evaporation condition) and non-stoichiometric method (stirring and shaking conditions) respectively, whereas in propanol, Form A formed from stirring and evaporation conditions while Form B formed from shaking conditions. Fig. 2 shows the pattern profile for both Form A and Form B from all methods in ethanol.

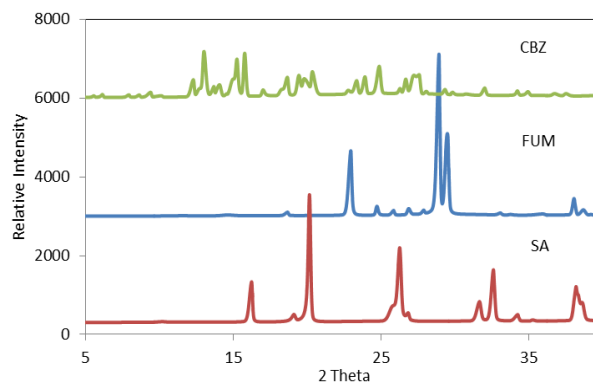


Fig. 1. PXRD pattern profile for pure components.

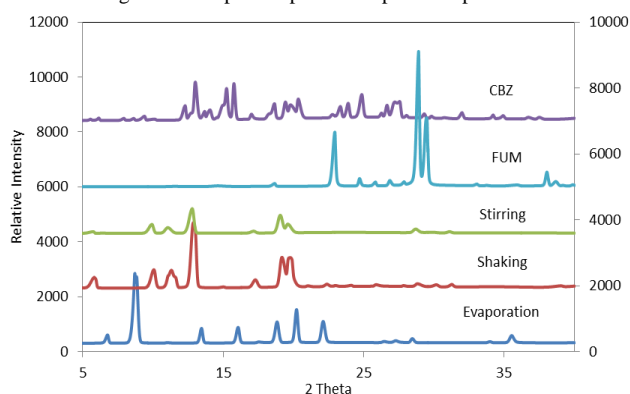


Fig. 2. PXRD pattern profile for stoichiometric (Form A co-crystal) and non-stoichiometric (Form B co-crystal) in ethanol as a solvent.

Fig. 3 shows the diffraction pattern for CBZ-SA co-crystal in different solvents system. Based on the patterns, diffraction peaks for CBZ-SA in all solvent matched with previous studied conducted by other scholars by  $\pm 10\%$  deviation [23], [30], [31] and does not contain any diffraction peaks of pure components of CBZ and SA which confirms that the powder sample measured was a co-crystal except for formic acid. There were some pattern peaks found in formic acid solvent system that similar to succinic anhydride [26] and CBZ-formic acid solvate [32], therefore it was suspected that there were mixture of both components in the solvent system. However, there is significant different between patterns produced using non-stoichiometric and stoichiometric methods. Solvent evaporation method yields more sharp and prominent peaks due to crystalline nature of the co-crystal produced no agitation and stirring effect involve during the crystallization process [18].

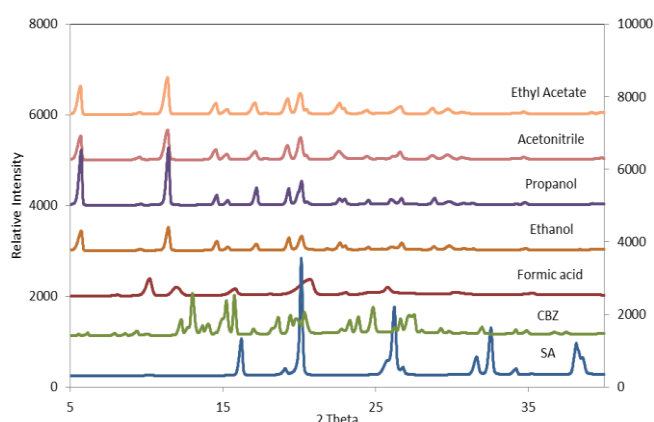


Fig. 3. PXRD pattern profile for CBZ-SA co-crystal using non-stoichiometric (stirring) method.

Table I shows the summary of the overall analysis results including the co-crystals formed from acetonitrile, ethyl acetate, formic acid, ethanol and propanol. Table I indicated that the CBZ-FUM co-crystals were successfully formed except for formic acid from solvent evaporation method which was failed to yield either nor, CBZ, FUM and co-crystal. This is presumably that the solubility of CBZ in the solvent medium directly affected the formation of the CBZ, FUM or co-crystal that required as an optimum condition to induce the precipitation of the crystal in solvent evaporation. Meanwhile, CBZ-SA co-crystals were not formed only in formic acid by both methods.

#### B. Differential Scanning Calorimetry (DSC)

Based on Fig. 4, the melting point obtained for FUM and SA were  $293^{\circ}\text{C}$  and  $187^{\circ}\text{C}$  respectively. For CBZ, there is an endothermic peak at  $172.19^{\circ}\text{C}$  follow by another peak at  $191^{\circ}\text{C}$ . Polymorphic transformation of CBZ from Form III to Form I best described the thermal event where polymorphic transformation take place at  $162\text{--}175^{\circ}\text{C}$  and new phase melted at  $189\text{--}193^{\circ}\text{C}$  [17] which  $191^{\circ}\text{C}$  represent melting point of CBZ Form I. This proved that DSC was important in co-crystal characterization as well as polymorphic characterization, since different polymorph has different melting point.

TABLE I: SUMMARY RESULTS FOR STOICHIOMETRIC AND NON-STOICHIOMETRIC METHOD

Solvent	Screening Method	CBZ-FUM Form A	CBZ-FUM Form B	CBZ-SA
Acetonitrile	Stirring	✓		✓
	Shaking	✓		✓
	Evaporation	✓		✓
Ethyl acetate	Stirring	✓		✓
	Shaking	✓		✓
	Evaporation	✓		✓
Formic acid	Stirring		✓	
	Shaking		✓	
	Evaporation			
Ethanol	Stirring		✓	✓
	Shaking		✓	✓
	Evaporation	✓		✓
Propanol	Stirring	✓		✓
	Shaking		✓	✓
	Evaporation	✓		✓

CBZ-FUM co-crystal Form A has melting point in the range of  $172\text{--}176^{\circ}\text{C}$  [21], while Form B at  $186\text{--}190^{\circ}\text{C}$  [23], [28], [29]. The increasing in melting point of the two forms possibly due to the crystal packing nature in the CBZ-FUM co-crystal [33]. CBZ-FUM Form A has an additional endothermic peak at  $116\text{--}126^{\circ}\text{C}$  which indicate the present of water molecule in the co-crystal [28]. Meanwhile, CBZ-SA co-crystal produced has melting temperature of  $188^{\circ}\text{C}$  as shown in Fig. 5. However, additional peak at  $120^{\circ}\text{C}$  occurs for system using formic acid as solvent suggested the existence of succinic anhydride and CBZ-formic acid solvate in the system.

#### C. Fourier Transform Infrared (FT-IR)

Table II represent the summary of peak position in the co-crystal compare with the pure component for propanol solvent. The characteristic peaks of CBZ were observed at  $3464$ ,  $1677$ ,  $1604$  and  $1593\text{ cm}^{-1}$ , compatible with reference [16], [17]. The analysis of FTIR spectrum for CCF revealed peaks at  $1659\text{ cm}^{-1}$  and  $3082\text{ cm}^{-1}$  for FUM whereas  $1676\text{ cm}^{-1}$  and  $2931\text{ cm}^{-1}$  which were assigned to SA  $\beta$  polymorph [34].

CBZ-SA exhibit wavelength at  $3471$ ,  $1698$ ,  $1629$  and  $2790\text{ cm}^{-1}$ , that were in good agreement with the previous [35]. The rest of the solvents and methods used show similar result except for formic acid in all methods. For this solvent, several distinct IR peaks were observed at  $3440\text{ cm}^{-1}$  (amide N-H stretch),  $3316\text{ cm}^{-1}$  (C-H stretch, alkene),  $1694\text{ cm}^{-1}$  (C=O) and  $1633\text{ cm}^{-1}$  (C=C) that suggested the existence of CBZ-formic acid solvate [32].

The peak profiles in FT-IR spectrum for CBZ-FUM co-crystal was either higher or lower compared to the pure component. The formation of co-crystal can be confirmed by the significant shifting of wavelength [33], [36]. For CBZ-FUM Form A, the peak attribute to the N-H stretch has been shifted to  $3455\text{ cm}^{-1}$ ,  $1705\text{ cm}^{-1}$  (C=O),  $1601\text{ cm}^{-1}$  and  $1590\text{ cm}^{-1}$  (N-H bend) for amides meanwhile  $3059\text{ cm}^{-1}$  (O-H stretch) and  $1656\text{ cm}^{-1}$  (C=O) for carboxylic acid. In addition, for CBZ-FUM Form B, the peak for amides have shifted to  $3461\text{ cm}^{-1}$  (N-H stretch),  $1682\text{ cm}^{-1}$  (C=O),  $1601\text{ cm}^{-1}$  (N-H bend) whereas for carboxylic acid show peaks at  $3052\text{ cm}^{-1}$  (O-H stretch) and  $1629\text{ cm}^{-1}$  (C=O).

TABLE II: FT-IR DATA FOR CBZ, FUM, SA AND CO-CRYSTAL BASED ON DIFFERENT SCREENING METHOD USING PROPANOL

Functional group	CBZ	FUM	SA	CBZ-FUM co-crystal			CBZ-SA co-crystal		
				Shaking	Stirring	Evaporation	Shaking	Stirring	Evaporation
Amides									
N-H Stretch	3464	-	-	3461	3457	3455	3470	3471	3468
C=O Stretch	1677	-	-	1679	1706	1706	1698	1698	1698
N-H Bend	1604	-	-	1601	1602	1602	1629	1629	1627
	1593				1591	1590			
Carboxylic acids									
O-H Stretch	-	3082	2931	3052	3057	3059	2789	2790	2789
C=O Stretch	-	1659	1676	1627	1660	1656	1698	1698	1698

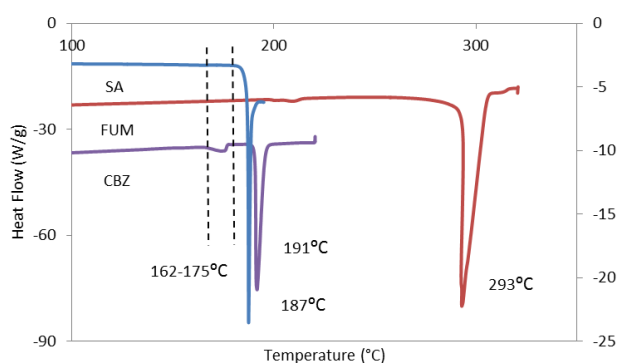


Fig. 4. DSC analysis for pure components of CBZ, FUM and SA.

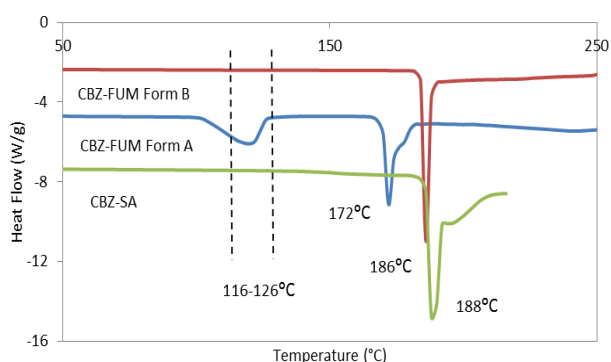


Fig. 5. DSC analysis for shaking in ethyl acetate (CBZ-FUM Form A and CBZ-SA) and shaking in propanol (CBZ-FUM Form B).

#### IV. CONCLUSION

The formation of CBZ-FUM and CBZ-SA co-crystals were investigated using non-stoichiometric (continuous shaking and stirring) and stoichiometric (solvent evaporation) methods. The PXRD analysis had confirmed that the CBZ-FUM and CBZ-SA co-crystals were successfully formed in both methods for all of the solvents systems studied with an exception to formic acid in the stoichiometric method for CBZ-FUM system and in all methods for CBZ-SA system. From this analysis it was also shows that CBZ-FUM co-crystal Form A and Form B had been produced from different solvents. This shows that further study in screening is needed for co-crystal formation assessment since there were already many factors proven in affecting the polymorphic transformation of the co-crystal such as different methods,

solvent and mole ratio.

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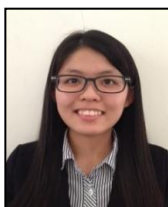
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