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Research paper



Effect of Solvents and Crystallization Methods on the Formation of Carbamazepine-Saccharin Co-Crystal

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Abstract

Active Pharmaceutical Ingredients (API) crystallized in its co-crystal form is believed to be able to improve the physicochemical properties of its pure crystal. Carbamazepine (CBZ) and saccharin (SAC) were used in this study in investigation of effect of solvents and crystallization methods on the formation of CBZ-SAC co-crystal. There were four different solvents (acetonitrile, ethanol, ethyl acetate and propanol) and two crystallization methods (slurry and stirring crystallization) used in this study. The crystals produced were characterized by Differential Scanning Calorimetry (DSC), Powder X-Ray Diffraction (PXRD), Fourier Transform Infrared (FTIR) and optical microscopy. The findings revealed that only Form I of CBZ-SAC co-crystals was successfully formed for all parameters under studied. It was concluded that the type of solvents, crystallization methods and CBZ:SAC ratio used in this study did not play an important role on the CBZ-SAC Form I co-crystal formation for this system.

Keywords: *Carbamazepine; Co-crystal; Polymorphic; Saccharin, Screening*

1. Introduction

In pharmaceutical industry, crystallization process of polymorphs and solvated crystals need to be controlled as it can affect the bioavailability, stability, solubility, and morphology of pharmaceutical products [1]. Crystal form is very important in determining the performance of a dosage form [2]. This is true for compounds that restricted in drug delivery such as low aqueous solubility, slow dissolution in gastrointestinal media and low permeability.
Carbamazepine (CBZ) is one of the water insoluble drugs used for over 30 years as an anti-epileptic agent and requires high dosage for therapeutic effect. CBZ has four anhydrous polymorphic forms and can form as solvates and dihydrate from aqueous solutions [3, 4]. Saccharin (SAC) is a sweetener and one of the most popular co-crystal former (CCF) for producing new pharmaceutical co-crystals and a well-known co-former to form 1:1 ratio in co-crystal lattice with CBZ [4].
Solvent is one of the factors that affecting the formation of co-crystal forms [5] and sometimes resulted in polymorphic changes of CBZ [6]. In addition, final crystal products such as crystal size and morphology also can be affected by the choices of solvent [7,8]. The effect of solvent on crystallization processes is crucial for understanding and developing methods to determine crystal forms [9]. Methods used for co-crystallization process also played an important role in determining the polymorphism of co-crystal produced such as antisolvent [10], polymer-assisted hetero-nucleation approach [11] and fast evaporation [12]. Nonetheless, there is no single promising method can produce a stable form of a given compound and thus initiated the methods chosen in this screening process.

The objective of this study is to assess the CBZ-SAC co-crystals form from various stoichiometric ratios between API and CCF in different solvent systems (acetonitrile, ethanol, ethyl acetate and propanol). The methods of crystallization used in this study were stirring and slurry crystallization methods.

2. Materials and methods

2.1. Chemicals

Carbamazepine (CBZ) and saccharin (SAC) were obtained from ECA Corporation USA and Sigma Aldrich, respectively. Absolute ethanol (EtOH 99.4 %), acetonitrile, ethyl acetate and propanol were obtained from Fisher Scientific Malaysia and used as the solvent in producing co-crystals.

2.2. Experimental methods

The experimental works were conducted using slurry and stirring crystallization methods. Ten mol ratios of SAC/CBZ were prepared starting from 0.5 mol and the rest of samples from 1.0 to 3.0 mol are with the interval of 0.25 mol each. The crystals produced from the crystallization experiments then were filtered using vacuum filter at room temperature before undergo characterization analysis.
In slurry crystallization method, mixture of both pure components with a known mol ratio was slurried in a conical flask with 10 mL of ethanol and stirred in orbital shaker for 72 hours at room temperature. While for stirring crystallization method, a mixture of CBZ and SAC were stirred in 10 mL of ethanol in a vial with magnetic stirrer for 72 hours at room temperature.

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2.3. Characterization analysis

Differential Scanning Calorimetry (DSC) Q1000 was used to determine the melting point of the crystal. For a uniform thermal contact with the crucible pan, a mortar and pestle was used to ground the sample crystals. The sample was weighed to between 2 and 3 mg in standard aluminum pan and analyzed in the DSC from 25 to 300°C with heating rate of 10°C/min.
Powder X-Ray Diffraction (PXRD) (RIGAKU (Miniflex ii)) was used to identify the powder pattern profile of the sample. A copper X-ray tube was used to generate the X-rays, which operated at 30 kV and 15mA. The angular range used was from 5° to 40° for 2θ (angle). The step size and step time were 0.01 and 1 second/step, respectively.
Fourier Transform Infrared (FTIR) (Thermo Scientific) was used to identify the presence of specific functional groups of the molecule. Spectra were collected in the range of 4000-600 cm^{-1} using 32 scans per spectrum with a resolution 4 cm^{-1} for each sample was used for the analysis.
Optical microscopy was used to observe the shape of the crystals obtained. Optical microscopy with magnification of 5x was used to observe the morphology of the co-crystals.

3. Results and discussion

3.1. Differential scanning calorimetry (DSC)

Melting point of the pure components and co-crystal produced were determined by DSC. Fig. 1 shows the DSC results for CBZ, SAC and CBZ-SAC co-crystal. The melting point of SAC was 227°C [13]. For CBZ, the endothermic peak at 172°C represents the transformation of CBZ Form III to Form I in which 191°C is the melting point of CBZ Form I [3].
The polymorphic forms of co-crystal can also be determined by mol ratios of CCF/API [14]. All resulted solid crystals show melting point in the range of 173-177°C, which indicate the formation of CBZ-SAC co-crystal Form I [10-12, 15]. However, there is an additional peak at 158-160°C for crystal obtained from propanol solvent system using slurry method (i.e. stoichiometric ratios: 1.25-3.00), stirring method (i.e. stoichiometric ratio: 0.50) and from ethyl acetate solvent system of the stirring method (i.e. stoichiometric ratio: 3.00). This peak suggests the formation of CBZ phase at the initial crystallization process [10]. Other crystalline samples produce peak at 224-230°C, which indicate the existence of pure SAC in final crystal formed are summarized in Table 1.

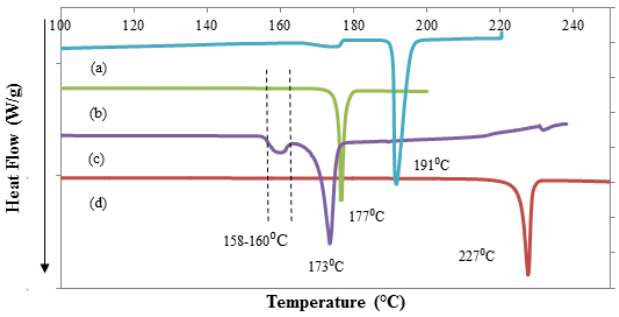


Fig.1: PXRD pattern profile for (a) pure CBZ; (b) SAC: CBZ (1.50:1.00) in ethanol solvent for stirring method; (c) SAC:CBZ (3.00:1.00) in propanol solvent for slurry method; (d) pure SAC.

3.2. Powder x-ray diffraction (PXRD)

The pattern profiles from PXRD were compared between the pure components and solid crystal produced, as shown in Fig. 2. The pattern profile for pure component CBZ is compatible to the polymorph of anhydrous CBZ Form III [3], while the SAC profile peak shown in this work is in a good agreement with reported by previous study [16].

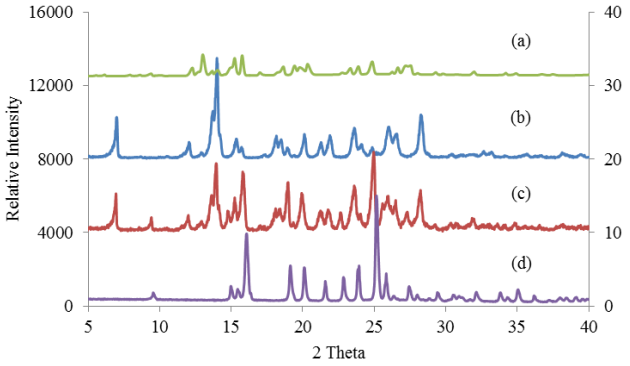


Fig. 2: PXRD pattern profile for (a) pure CBZ; (b) SAC : CBZ (1.50 : 1.00) in ethanol solvent for stirring method; (c) SAC : CBZ (3.00 : 1.00) in propanol solvent for slurry method; (d) pure SAC.

CBZ-SAC co-crystal Form I has successfully formed in all solvents using both methods [4, 17]. However, crystals grown in propanol and ethyl acetate show additional peaks at 9.4°, 22.7° and 27.4°, and three consecutive peaks at 14.8°, 15.4° and 16° which indicate the presence of pure SAC in the samples (refer Fig. 1(c)). The DSC results also show an additional peak in the analysis which corresponds to pure SAC. This result also reflects that possibly that the CBZ phase transformation does not takes place in propanol and ethyl acetate. Strong diffraction peaks at 4.9° and 14.9°, which are used to identify the CBZ-SAC co-crystal Form II [11], are not visible in all samples diffraction in this study.

Table 1 summarizes the results for co-crystals recovered from various stoichiometric ratios, methods and solvents used in this study. However, for some ratios: (1) stoichiometric ratios: 0.50 for acetonitrile, ethanol and ethyl acetate in slurry method, and for ethyl acetate in stirring method; and (2) stoichiometric ratios: 0.50-1.00 for acetonitrile in stirring method, insufficient solid crystals were produced due to small quantity of pure components used at the beginning of the experiment, and hence no result can be reported for this ratio. In slurry method, 100% conversion CBZ-SAC co-crystal can only be formed in 1.00 stoichiometric ratio for acetonitrile, while for ethanol and propanol solvent, the co-crystal can be formed from solution with CBZ:SAC ratio up to 2.00 and 1.50 ratios respectively. The solution with higher ratios also can form co-crystal but the SAC crystals were also detected and present as a solid mixture. This probably due to the solution already reached SAC solubility limit and no longer could dissolve in the solution and precipitated out. Crystal grown in ethyl acetate using slurry method shows mixtures of both co-crystal and pure SAC in their final product. Meanwhile, for stirring method, the mixture of both components were found to form in 2.00 ratio in acetonitrile, 2.25 ratio in ethyl acetate and 2.50 ratio and above in ethanol. For all ratios, crystals produced in propanol and using stirring method formed mixtures of co-crystal and pure SAC. The best crystallization method to produce co-crystal is by stirring method as CBZ-SAC co-crystal are able to be formed in solution with higher ratios without the presence of pure components crystals, compared to slurry method. Meanwhile, ethanol is the best solvent to be used as pure SAC more soluble in this solvent compared to the other solvents used.
Therefore, from DSC and PXRD analysis, it can be concluded that only one polymorph are successfully formed in this study which was CBZ-SAC co-crystal Form I. Thus, mol ratios, solvents and methods used in this study did not play an important role in polymorphism changes of CBZ-SAC co-crystal. However, other methods and solvents can be used to further study the polymorphs of co-crystal as it has been reported that polymorph changes in CBZ-SAC co-crystal occurred in different method [20] and additional of polymer [11].

Table 1: Summary of results for slurry and stirring crystallization method

Methods	Mol ratio (SAC/CBZ)	Solvent							
		Acetonitrile		Ethanol		Ethyl acetate		Propanol	
		CBZ-SAC Form I	pure SAC	CBZ-SAC Form I	pure SAC	CBZ-SAC Form I	pure SAC	CBZ-SAC Form I	pure SAC
Slurry	0.50	-	-	-	-	-	-	√	-
	1.00	√	-	√	-	√	√	√	-
	1.25	√	√	√	-	√	√	√	-
	1.50	√	√	√	-	√	√	√	-
	1.75	√	√	√	-	√	√	√	√
	2.00	√	√	√	-	√	√	√	√
	2.25	√	√	√	√	√	√	√	√
	2.50	√	√	√	√	√	√	√	√
	2.75	√	√	√	√	√	√	√	√
	3.00	√	√	√	√	√	√	√	√
Stirring	0.50	-	-	√	-	-	-	√	√
	1.00	-	-	√	-	√	-	√	√
	1.25	√	-	√	-	√	-	√	√
	1.50	√	-	√	-	√	-	√	√
	1.75	√	-	√	-	√	-	√	√
	2.00	√	√	√	-	√	-	√	√
	2.25	√	√	√	-	√	√	√	√
	2.50	√	√	√	√	√	√	√	√
	2.75	√	√	√	√	√	√	√	√
	3.00	√	√	√	√	√	√	√	√

3.3. Fourier transform infrared (FTIR)

Fig. 3 shows the FTIR results captured in this study, in which the presence of functional groups in a molecule can be determined by FTIR. The analysis of FTIR spectrum for CBZ Form III used in this study reveals peaks at 1675 cm^{-1} (C=O stretch), 1604 cm^{-1} due to vibration of (C=C) and (C=O) and 1593 cm^{-1} (N-H bend) [3,19]. Pure component SAC exhibits wavelength at 3088 cm^{-1} (N-H stretch), 1714 cm^{-1} (C=O stretch), and 1331 and 1173 cm^{-1} (-SO_2 stretch) [20, 21]. A peak shift seen in Fig. 3 could corresponds to N-H stretch of the amide from 3464 cm^{-1} for CBZ to 3494 cm^{-1} for the CBZ-SAC co-crystal Form I. Comparison of the spectrum of SAC and CBZ-SAC co-crystal shows a peak corresponding to asymmetrical stretch of -SO_2 from 1331 cm^{-1} in the spectrum of SAC to 1326 cm^{-1} in the spectrum of co-crystal, and the other characteristic peak of co-crystal Form I is 1642 cm^{-1} (C=O stretch).

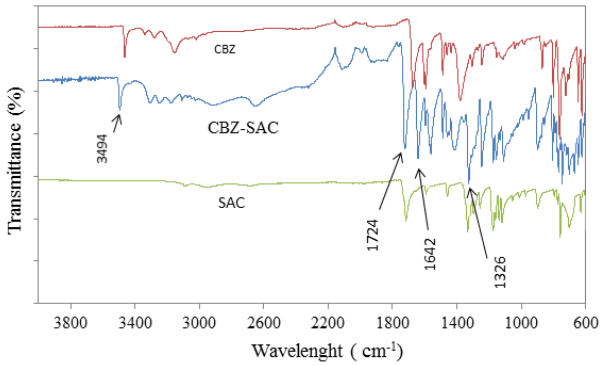


Fig. 3 FTIR spectra for CBZ, SAC and CBZ-SAC co-crystal

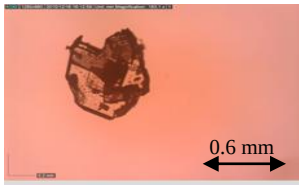
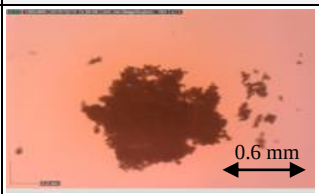
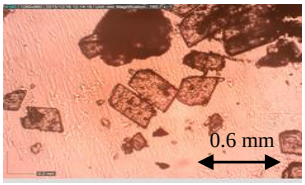
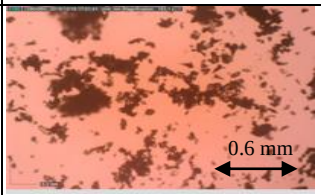
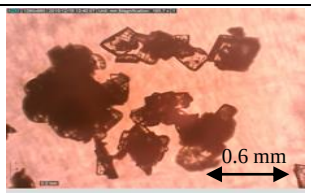
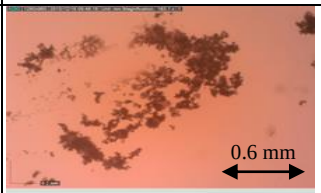
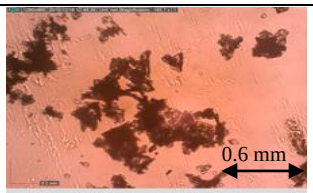
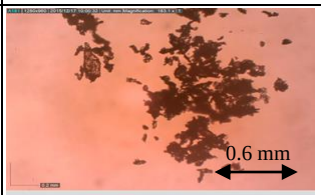
3.3. Optical microscopy

Morphology of the co-crystal was determined by using optical microscopy and the pictures captured in this study is shown in Table 2. The shapes of the obtained crystals are plate-like for all samples which correspond to CBZ-SAC Form I, and in agreement to the findings by previous researchers [17, 18]. The size of co-crystals in stirring method are much smaller compared to crystals obtained from slurry method, probably due to the mixing condition during crystallization process, in which stirring with magnetic stirrer was more vigorous than shaking with shaker [18].

4. Conclusion

In this study, the formation of CBZ-SAC co-crystal in slurry and stirring method in different solvent system (acetonitrile, ethanol, ethyl acetate and propanol) were investigated. The PXRD analysis had confirmed the CBZ-SAC co-crystals Form I were successfully formed by both methods in all solvents system. Both methods are capable of producing CBZ-SAC Form I co-crystals. Therefore, type of solvents, crystallization methods and CBZ:SAC ratio used did not play an important role in determining the polymorph form of CBZ-SAC co-crystal for this system.

Table 2: Optical micrographs detailing the crystal morphology for SAC:CBZ (1.25:1.00). The magnification used was 5x.

Solvents	Slurry method	Stirring method
Acetonitrile		
Ethanol		
Ethyl acetate		
Propanol		

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