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Crystallisation parameters effect on the particle size distribution (PSD) of carbamazepine-saccharin (CBZ-SAC) co-crystals in batch cooling crystallisation

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Abstract. The crystallisation parameters effect on the particle size distribution (PSD) of carbamazepine-saccharin (CBZ-SAC) co-crystals in batch cooling crystallisation is presented. The particle size distribution study of CBZ-SAC co-crystals revealed that the multimodal with broad PSD was found for CBZ concentration of 19.14 mg/ml. Meanwhile, the unimodal with broad PSD were observed at CBZ concentration of 17.01 mg/ml and 17.96 mg/ Crystal characterisation using differential scanning calorimetry (DSC), X-ray powder diffraction (XRPD), Fourier transform infrared (FTIR) and optical microscopy confirm the solid formed is CBZ-SAC co-crystal Form I with plate-like crystal morphology.

1. Introduction

Drug molecules with limited solubility are the major problems encountered by the pharmaceutical industry nowadays. Carbamazepine (CBZ) is a poorly water soluble drug that exists in different crystalline forms with different solubility, dissolution rate, and bioavailability. CBZ has the problems of its slow rate of absorption when administered through oral route in which a larger dose of the drug is needed in order to be effective to treat patients [1]. The co-crystallisation of CBZ with saccharin (SAC) has widely studied to improve the CBZ solubility [2, 3].

Crystallisation process is a widely used in pharmaceutical industries. The main challenge in the crystallisation process is to produce crystals with desired properties such as a polymorphic form, morphology and crystal size distribution [4]. The crystallisation process determines the chemical purity and physical properties of the product, as well as its habit, particle size and crystal structure [5]. The particle size of a drug substance can influence the final drug product performance such as dissolution, bioavailability, content uniformity, compatibility [6] and flowability [7]. The control of the PSD in pharmaceutical crystallisation is important since the particle size determine the quality of the final product and affect the downstream operations such as filtration and drying [8]. The control of crystallisation parameters is necessary in order to achieve the desired particle size distribution. This

paper reports on the influence of concentration of CBZ, mol ratio values of SAC/CBZ and cooling rates towards the particle size distribution of CBZ-SAC co-crystal using batch cooling crystallisation.

2. Materials and Methods

2.1. Materials
Carbamazepine (CBZ) and Saccharin (SAC) were obtained from UHN Shanghai and Sigma Aldrich, respectively. Absolute ethanol (EtOH 99.4 %) was used as solvent used for the formation of solid crystals.

2.2. Polythermal cooling crystallisation method
A Syrris 250 ml reactor equipped with a stirrer was used in the particle size distribution study of CBZ-SAC co-crystals. The parameters under studied were CBZ concentrations (17.01 mg/ml, 17.96 mg/ml and 19.14 mg/ml), mol ratios of SAC to CBZ (1:1, 1:1.5, 1:2, 1:2.5 and 1:3) and cooling rate (0.1, 0.25, 0.5, 0.75 and 1.0 °C/min) at a stirring speeds of 250 rpm.

The mixture of 1.0 SAC/CBZ mol ratio and 17.96 mg/ml of CBZ was heated to 60°C with 250 rpm of stirring speed for 1 hour to fully dissolve the solid. The mixture was cooled at a rate of 0.1°C/min. The co-crystal formed was filtered using vacuum pump at a room temperature prior to characterisation. Similar steps were repeated for the other parameters as stated earlier.

2.3. Characterisation of CBZ-SAC co-crystals
Particle size distribution of the produced co-crystal was measured by a laser diffraction using Malvern Instruments Mastersizer 2000 laser particle size analyser (Malvern, UK) combined with Scirocco 2000 as the dry powder feeder. A dry method was used to determine the particle size distribution with air as the dispersion agent. The data was presented in terms of D(0.5) which was defined as the mean crystal size.

The melting point of the produced co-crystal was determined using differential scanning calorimetry (DSC). A mortar and pestle was used to grind the crystal in order to get 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 300°C, with a flowrate of 50 ml/min of nitrogen gas purging at a heating rate of 10°C/min.

The produced crystal also being identified using x-ray powder diffraction (XRPD) using RIGAKU (Miniflex II) diffractometer with Cu Kα radiation. The system was run 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.

Fourier transforms infrared (FTIR) was used to determine the existence of functional groups in a molecule. The analysis for each sample was carried out using FTIR with 50 series model attached with the diamond detector at the wave number from 4000-600 cm^{-1} using 32 scans per spectrum with a resolution of 4 cm^{-1}.

The morphology of the crystals was observed using a Dino-eye microscope eyepiece and Carl Zeiss Model optical microscopy with 5x magnification.

3. Results and Discussion

3.1. Effect of crystallisation parameters on particle size distribution (PSD) of CBZ-SAC co-crystals
The particle size distribution (PSD) reported in terms of mean crystal size, D(0,5) of CBZ-SAC co-crystal obtained from the cooling crystallisation. The PSD decrease as the cooling rate increase from 0.1 to 1.0 °C/min. The trend is similar for all the CBZ concentrations and the SAC to CBZ ratio. The highest PSD (618.25 μm) has been obtained at the lowest cooling rate i.e 0.1 °C/min probably due to low supersaturation achieved at low cooling rate which result in the decreasing of nucleation and large mean crystal size [9].

The PSD of CBZ-SAC co-crystals for the cooling crystallisation reveals that the multimodal and broad PSD (Refer figure 1 and 2) were found at concentration of 19.14 mg/ml of CBZ at a cooling rate of 0.5 °C/min and above. The finding was applicable to all mol ratio of SAC to CBZ under studied with the exception to cooling rate 1.0 °C/min at 1.5 ratio of SAC to CBZ as the unimodal and broad PSD was obtained.
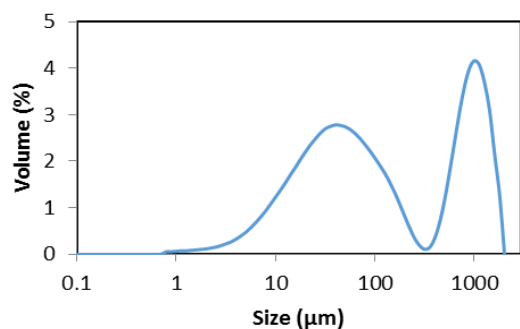

Figure 1. Multimodal and broad PSD curve for 19.14mg/ml of CBZ concentration, 1:2 mol ratio of SAC to CBZ and 0.75 ºC/min cooling rate.
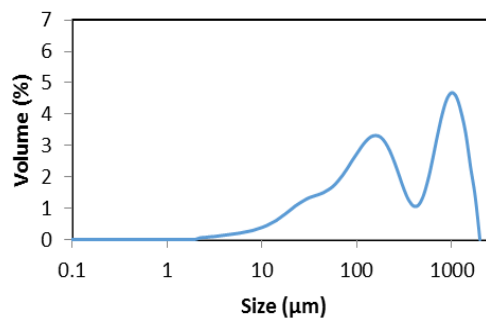

Figure 2. Multimodal and broad PSD curve for 19.14mg/ml of CBZ concentration, 1:3 mol ratio of SAC to CBZ and 0.75 ºC/min cooling rate.

This finding suggested that higher solute concentrations, results in supersaturation increase as the number of nuclei formed increases with the increasing of nucleation rate [10] thus, the precipitation of the solute occurs earlier as compared to lesser concentration. Higher solution concentration also means more molecules were present in the solution and results in higher probability of molecular collision [11]. This situation may increase the interaction between particles formed and resulted in the agglomeration of the crystal particles and lead to broadened of the PSD [12].

The unimodal and broad PSD (Refer figure 3 and figure 4) were observed at lower concentration of CBZ (17.01 and 17.96 mg/ml) applicable to all cooling rate and mol ratio of SAC to CBZ under studied except at concentration 17.01 mg/ml of CBZ at cooling rates of 0.5 and 1.0 °C/min for SAC to CBZ ratio of 2.5 where multimodal and broad PSD were observed. At lower solute concentrations, the crystal growth rate is slower and formed small crystals [13]. This could be the factor of the unimodal and broad PSD.
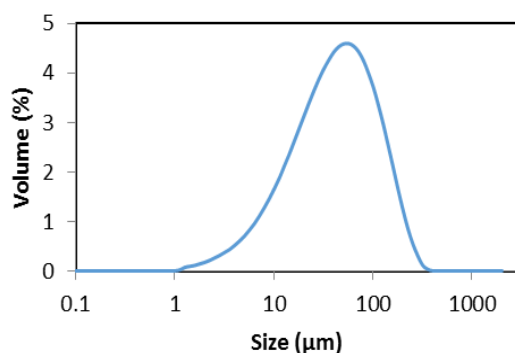

Figure 3. Unimodal and broad PSD curve for 17.01 mg/ml of CBZ concentration, 1:2 mol ratio of SAC to CBZ and 0.75ºC/min cooling rate.
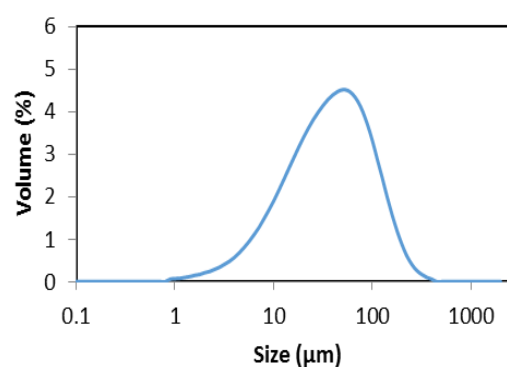

Figure 4. Unimodal and broad PSD curve for 17.96 mg/ml of CBZ concentration, 1:2 mol ratio of SAC to CBZ and 0.75ºC/min cooling rate.

3.2. Solid state characterisation of CBZ-SAC co-crystal

Figure 5 indicates the melting point of the CBZ, SAC and CBZ-SAC co-crystal. The DSC profile shows small and sharp peak for CBZ. The small peak at 172°C indicates the transformation of CBZ Form III to Form I where 191°C represent melting point of CBZ Form I [14]. The endothermic peak at 227°C reveals the melting point of SAC [15]. It also can be seen that there is a peak profile 177°C. This peak indicates the melting point of the CBZ-SAC co-crystal. The measured melting point of CBZ-SAC has the similar value with reported literature [16, 17]. This finding indicates the formation of CBZ-SAC co-crystals Form I.
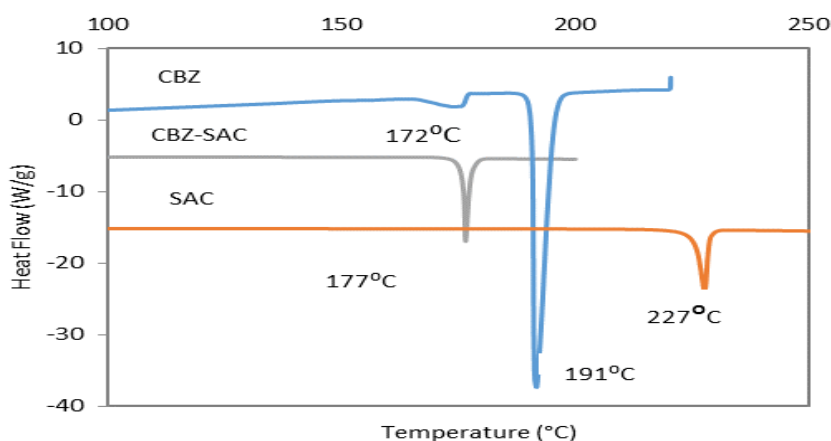

Figure 5. DSC profile showing the melting point of CBZ, SAC and CBZ-SAC co-crystal.

The PXRD pattern of CBZ, SAC and CBZ-SAC co-crystals is shown in figure 6. The peak occurs at $2\Theta = 15.3$, 19.4 and 24.9 indicates that this sample is a pure component of CBZ which was corresponds well with the polymorph of CBZ Form III reported [15]. The XRPD pattern also shows the pure component of SAC profile peaks occur at $2\Theta = 6.1$, 19.2 and 25.1 and is in agreement with reported literature [18,19]. The diffraction pattern at $2\theta = 7.04$, 14.1 and 20.1 is identical to the pattern reported previously which confirms the peak corresponds to the pattern profile of Form I CBZ-SAC co-crystal [17, 20, 21].

The FTIR spectra corresponding to the CBZ Form III is observed at 3466 cm^{-1} (N-H stretch) that correlate with the free anti N-H and hydrogen bonded syn-NH respectively [22]. A peak at 1676 cm^{-1} (C=O stretch) is also observed which is corresponding to the carbonyl stretch [23]. The CBZ Form III spectrum obtained agreed with previous study [23, 24, 25]. The peak shifted in the carbonyl, amide and SO$_2$ regions in the CBZ-SAC co-crystals spectrum, which correlate with hydrogen bond interactions in the crystal structure. The spectrum of pure SAC shows peak at 1722 cm^{-1} (C=O stretch) and 1334 cm^{-1} (-SO$_2$ stretch). The peaks matched to free carbonyl of SAC and hydrogen bonded carbonyl of CBZ are identified at 1730 cm^{-1} and 1,647 cm^{-1}, respectively in the CBZ-SAC co-crystals spectrum. There is also a peak shift corresponding to NH stretch of the amide from 3466 cm^{-1} for CBZ to 3502 cm^{-1} for the CBZ-SAC co-crystals. Comparison of the spectrum of SAC and CBZ-SAC co-crystals reveals a peak shift correlate to the asymmetric stretch of -SO$_2$ from 1,334 cm^{-1} in the spectrum of SAC to 1328 cm^{-1} in the spectrum of the CBZ-SAC co-crystals. The results are in agreement with other researchers [20, 23].
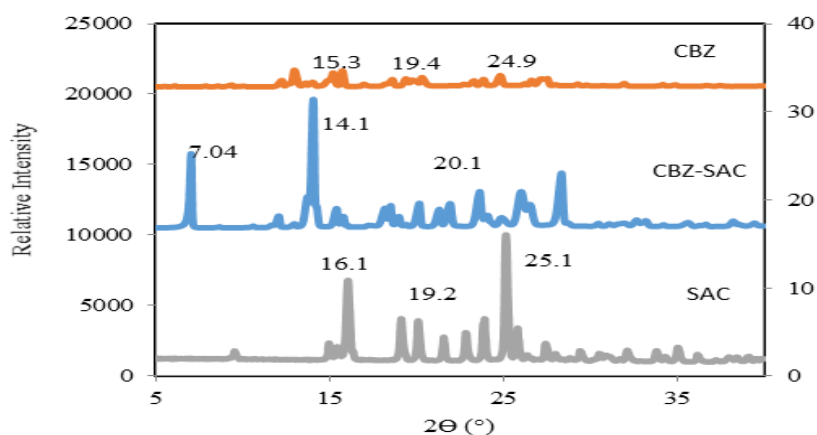
Figure 6. XRPD patterns profile of CBZ, SAC and CBZ-SAC co-crystals.

Morphological characterisation was used to observe the product crystals obtained from batch cooling crystallisation using optical microscopy with 5x magnifications. The morphology of the co-crystals obtained is shown in table 1. The result reveals that the CBZ-SAC co-crystals have the morphology of plate-like crystal for fast cooling crystallisation, and the same crystal morphologies were produced for all tested concentrations and cooling rates [2, 26]. The result also shown that the size of the crystal is mostly affected by the cooling rate. The bigger size of co-crystal is obtained at lower cooling rate (0.1 °C/min).

Table 1. Morphology of CBZ-SAC Co-Crystal with 5x magnifications.

Concentration (mg/ml)	Cooling rate (°C/min)				
	0.1	0.25	0.5	0.75	1.0
17.01					
17.96					
19.14					

4. Conclusions

The study on effects of crystallisation parameters on the particle size distribution (PSD) of carbamazepine-saccharin (CBZ-SAC) co-crystals was successfully carried out by cooling crystallisation with three different CBZ concentration, five different mol ratio of SAC to CBZ and five different cooling rate at 250 rpm. The PSD was found to be strongly affected by the solution concentration. The PSD study revealed that the multimodal and broad PSD was found at higher concentration of CBZ (19.14 mg/ml) whereas, unimodal and broad PSD were observed at lower concentration of CBZ (17.01 and 17.96 mg/ml). The characterisation analysis of CBZ-SAC co-crystals

through DSC, XRPD and FTIR has shown that the CBZ- SAC co-crystal Form I has formed with the morphology of plate-like crystal.

Acknowledgements

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