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Measurement of Carbamazepine-Succinic Acid (CBZ-SCA) Co-crystal Flowability

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ABSTRACT

In pharmaceutical industry, the bulk powder properties will have greater affect during processing, leading to the significant financial losses if action on controlling the problems is not in place. In this study, the effects of particle size and morphology on powder flow properties of the carbamazepine-succinic acid (CBZ-SCA) co-crystal were investigated using a Dietmar Schulze Shear Cell tester. Result shows that CBZ-SCAhas a mean size of below 100 μm and has easy flowing powder behaviour.

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INTRODUCTION

Industries dealing with powder processing need to know the particle size of the powder because this is one of the factors used to assess or to characterize the bulk properties of powders. In pharmaceutical industries, for example, it is important to know the particle size distribution and shape of an API or drug formulated, because this can be an indicator of flowability behaviour (Liu, L. X., 20081). The flowability behaviour are described refer to a range of flow factor, ffc given in Table 1.

Table 1: Powder flow behaviour used to describe the flowability (Schulze, D., 2008).

Flow factor range, ffc	Flowability description
ffc< 1	Not flowing
1<ffc<2	Very Cohesive
2<ffc<4	Cohesive
4<ffc<10	Easy flowing
ffc>10	Free flowing

In this study, co-crystal of CBZ-SUC was chosen as a material for flowabilitymeasurement. Co-crystals, in pharmaceutical context, can be defined as molecular crystalline complexes, which contain therapeutic molecules, where the co-crystal former and pharmaceutical agents (API) are usually bound together in the same crystal lattice. Both co-crystal former and API are in their pure forms and solid at ambient conditions. In contrast to salt, co-crystal can be formed even when the ionisable site of the API does not exist (Morissette, S. L., 2004, McMahon, J. A., 2005). In this case, CBZ is an API and SUC in a co-crystal former.

The crystal properties of the co-crystal can be expected to differ when compared to those of the pure forms. Optimal design of these co-crystals can be used to optimize the physical properties of pharmaceutical materials (McMahon, J. A., 2005). It has been reported that pysicochemical and pharmaceutical properties, such as dissolution rate and solubility of the single component crystal of a drug have been improved (Childs, S. L., 2004, Trask, A.V., 2005).

The majority of the compounds in pharmaceutical occurs as crystalline solids and usually are dosed as solid oral dosages, such as powders, capsules or tablets. Therefore, knowledge of flowability behaviour of a compond is necessary. Thus, thispaper seeks to examine the particle size distribution and flowability of the CBZ-SCA co-crystal powder produced from the crystallisation process.

MATERIALS AND METHODS

Materials:

All materials used in this study were procured from Sigma-Aldrich Company and had a purity exceeding 99%.

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Experimental methods:

Crystallisation process for CBZ-SCA co-crystals:

The experimental equipment used for the crystallisation experiment conducted to produce CBZ co-crystal in a quantity suitable enough for a flowability test consisted of a jacketed glass 1000ml reactor equipped with a stirrer, temperature and a condenser. The temperature within the reactor was maintained by a jacket fed from an external water bath. The system was capable of allowing the detection of particles by the human eye (clear glass reactor). A solution was prepared by adding the appropriately weighed solute using a balance with accuracy of +/- 0.01g, to the crystalliser, before heating the mixture to approximately 65°C and the temperature maintained constant for 60 minutes in the crystalliser to ensure that all the crystal solid had been fully dissolved. The solution was then cooled down to crystallise until room temperature, approximately 25°C. To isolate the solid co-crystal, the final solution was filtered using a vacuum and dried at room temperature.

Flowability determination for CBZ-SCA co-crystal:

The Flowability of the CBZ-SCA co-crystal systems was measured using a Ring Shear Cell called Dietmar Schulze Shear Cell. The main part of the Schulze RTS-XS ® Shear Tester is an annular cell, where the powder specimen is placed and covered by a lid to prevent powder slipping against the cell boundaries during shearing. The lid is subjected to a vertically acting normal force in order to attain the desired compression level during the test. For the purpose of this study, the normal force used was 2 kPa, 3 kPa and 4 kPa. A series of vanes is provided on the bottom of the cell and on the lid to spread out the powder to enable the shear formation of the powder sample when subjected to the rotational movement of the shear cell relative to the lid. This is achieved by two tie rods connected to the lid of the annular cell in addition to the load beams. The shear stress acting on the assembly is continuously monitored by these two additional load beams.

CBZ-SCA Co-crystal Characterisation:

The samples (co-crystals) obtained were characterised using microscopy techniques, DSC, and PXRD techniques to ascertain and/or confirm the solid form of co-crystal structure. Whereas, the particle size distributionsmeasurement was conducted using Morphology G3.

Morphology:

The morphology of the crystal is visible using microscopy. In this study an Olympus BX51 model microscope at magnification of 5x and 10x was used to observe the shapes of the crystals obtained from the crystallisation process.

Differential Scanning Calorimetry (DSC):

The melting point of the crystals was determined using a Mettler Toledo DSC model 820 fitted with a TS0801RO model automated sample robot. The sample crystal was ground using a mortar and pestle to obtain a thin sample for a better and more uniform thermal contact with the crucible pan. A small amount of sample was weighed using a 4 decimal place weighing balance in 40 micro-litre aluminium crucibles. The prepared crucible pan was sealed with a crucible lid. Using a pin, a small hole was made in the top of the crucible lid. The weights of the sample and the crucible pan with lid were noted. The plan used in the DSC measurement comprised of equilibrating the sample for 10 minutes at 25 ^{0}C, followed by heating at a specified rate to final temperature and 10 minutes equilibrating the sample at the final temperature. The rate used in this study was 10 degrees per minute.

X-Ray Powder Diffraction (XRPD):

XRPD patern profile was collected using Bruker AXS D8 Advance-Series 2 X-ray Diffractometer and a silicon type sample holder was used for the measurement. The sample used for measurement was ground using a mortar and pestle in order to obtain a fine crystal powder. The type of diffractometer to generate the X-rays used was a copper X-ray tube, which operated at 40 kV and 40mA. The plan used was from 5^o to 40^o for 2θ (angle). The step size and step time were 0.01 and 1 second/step, respectively.

Determination of Crystal Size Distribution and shape for CBZ-SCA Co-crystal:

The size distribution of the CBZ-SCA co-crystal systems was measured using Particle Characterisation Image Analyser Moprphology G3. The main part of the Morphology G3 is the precision XY stage, confined on a glass plate for sample scanning on which the powder sample is dispersed. The sample was tumbled in its container and transferred to the integrated Sample Dispersion Unit (SDU) using the 11mm^{3}spatula. The sample was placed in the holder and held by 6 µm metal foil. Air pressure of 0.8 bar was used to break the foil, and, as a result, the powder particles dispersed on the glass plate at that stage. The sample was assessed using 5x magnification of automated microscope optics.

RESULTS AND DISCUSSION

CBZ-SCA Co-crystal Characterisation:

Morphology:

Fig. 1 show the elongated needle-like morphology of the CBZ-SCA co-crystal obtained from the crystallisation process.

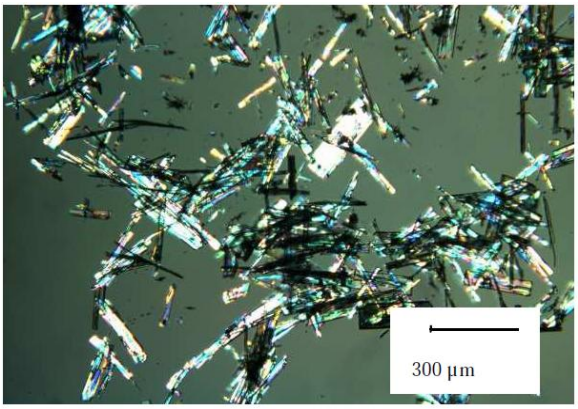

Fig. 1: CBZ-SCA co-crystal morphologytaken using 5x magnification optical microscope.

Differential Scanning Calorimetry (DSC):

The melting point of the CBZ-SCA co-crystals studied was recorded to be 189.5 ^{o}C in comparison to the initial pure components melting point with SCA at 188.7^{o}Cand CBZ at 178^{o}C and 191^{o}C. The two melting point obtained from CBZ confirmed that it wasCBZ form lll (Grzesiak, A. L., 2003, Gabbott, P., 2008). The fact that the melting point of the co-crystals is lower than, greater than or between the melting points of the pure components can be attributed to the nature of the intermolecular packing within the crystal packing lattice, composition and crystal structure (Walsh, R. D. B., 2003, Huang, N. C., 2011).

X-Ray Powder Diffraction (XRPD):

The results obtained from this XRPD is shown in Fig. 2. In the figure, the comparison is made between the peaks profiles of pure component with the product produced from the crsytallisation experiment and it shows the co-crystal co-crystal is successfully formed.

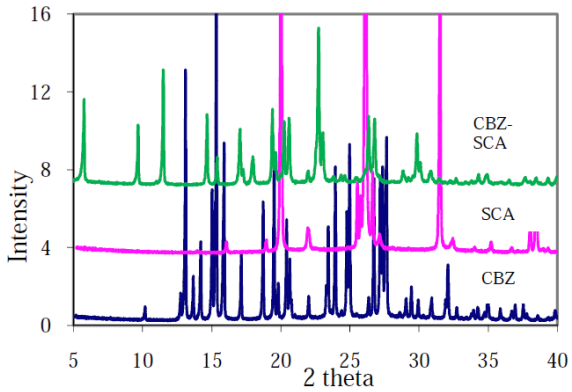

Fig. 2: XRPD pattern profile for CBZ-SCA co-crystal, SCA and CBZ.

Determination of Crystal Size Distribution for CBZ-SCA Co-crystal:

Theparticle size distribution and shape of the CBZ co-crystal are important in powder processing involving flowability and behaviour of tableting and compaction (Liu, L. X., 2008, Guo, A., 1985, Sun, C., 2001, Yu, W., 2011). In addition, the final product performance, such as drug delivery, dissolution behaviour and efficiency are also affected (Jinno, J., 2006). The results from the measurement are described as mean size, median(d_{50}), d_{10} and d_{90}listed in Table 1 and revealed that 50% of the particles fall below the mean particle size.

Table 1: Particles size distribution (d_{10} - the size of particle below which 10% of the sample lies, d_{50} - the size at which 50% of the particles are smaller and d_{90} - the size of particle below which 90% of the sample lies) for CBZ-SCA Co-crystal

Mean size (µm)	d_{10} (µm)	d_{50} (µm)	d_{90} (µm)
31.13	5.00	11.64	87.38

Flowability determination for CBZ-SCA co-crystal:

Fig. 3 shows that CBZ-SCA is easy flowing for the entire load given since the fcc obtained from the analysis is in the range of 4<ffc<10. This finding was contradicted with the literature, which stated that, generally, particles with a size less than 100 µm are likely to behave as cohesive powder and very cohesive or unable to flow for the particles less than 10 µm (Liu, L. X., 2008, Gad, S.C., 2008). In addition, for smaller particle size, the contact surface area is larger, which results in difficulties for the powder to flow (Li, Q., 2014). From Table 1, we should expect that CBZ-SCA should behave as a cohesive powder since 50% of its particles have a size of about 11.64 µm; however, this situation did not happen in fact it behaved easy flowing for the entire load given.

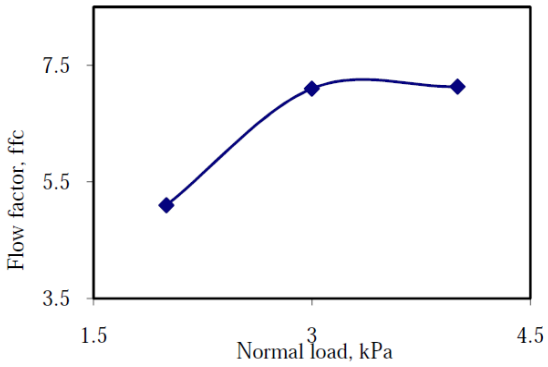

Fig. 3: Flow factor, ffc plot for CBZ-SCA co-crystals.

Conclusions:

This study presents morphology, particle size distribution and flowability of the CBZ–SCA co-crystal. The results show that CBZ-SCA co-crystal, has elongated needle-like morphology and mean size of 31.13 µm. Despite of having 50% of its particles has a size of 11.64 µm, CBZ-SUC demonstrated thatit has easy flowability behavior.

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