Supporting information

Drug Phase Transformation and Water Redistribution during Continuous Tablet Manufacturing – Case Study of Carbamazepine Dihydrate

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Analytical method for assessment of powder blend uniformity

Accurately weighed aliquot (~170 mg) of the powder blend was dispersed in 50 mL methanol in a 200 mL volumetric flask, and the volume was made up to 200 mL with deionized water. Ten mL of this solution was diluted to 250 mL to get an approximate concentration of 10 µg/mL. The solution was filtered (5 µm filter) and the absorbance at 284 nm was measured using a UV spectrophotometer. The calibration curve (Figure S1) was generated by preparing standard solutions in the range of 4 to 12 µg/mL The specificity of the method was confirmed by analyzing placebo samples.

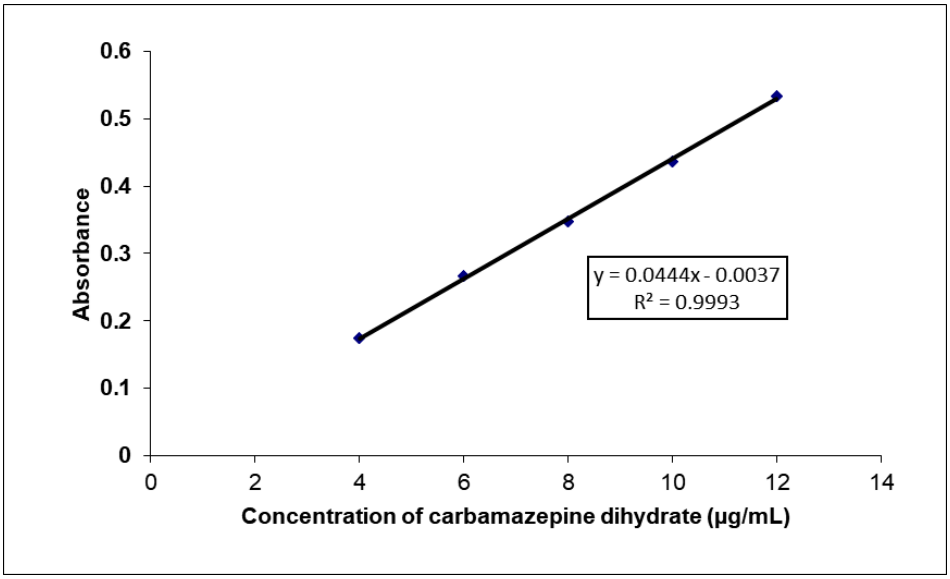


Figure S 1. The relationship between absorbance and concentration of carbamazepine dihydrate.

Baseline characterization of 'as received' API

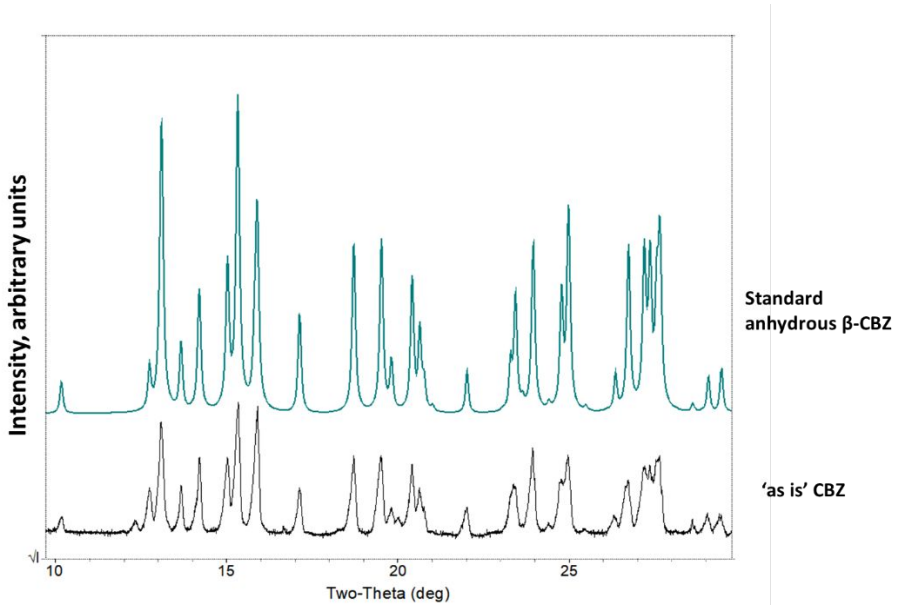


Figure S 2. XRD patterns of the 'as is' CBZ API plotted as an overlay with the standard pattern of anhydrous β-CBZ.

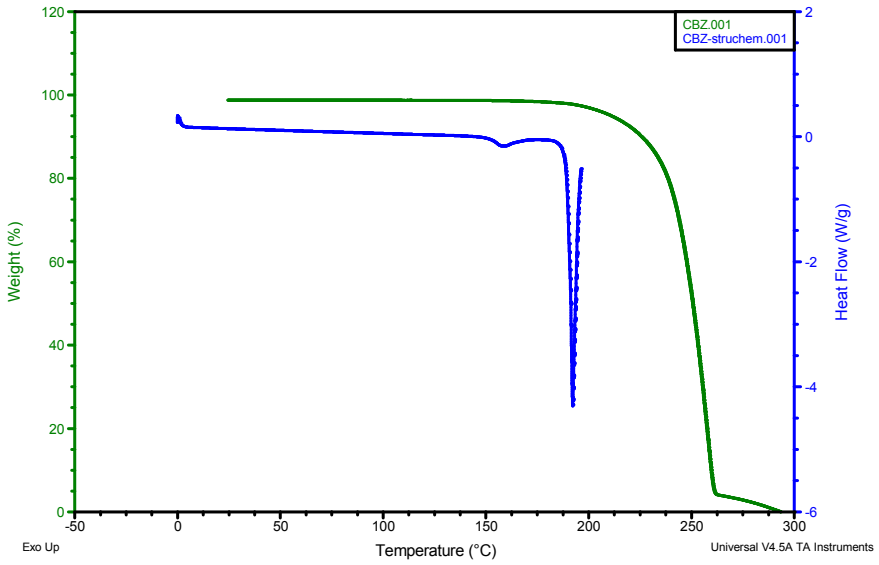


Figure S 3. DSC (blue curve) and TGA (green curve) heating curves of 'as is' anhydrous CBZ.

Baseline characterization of prepared CBZDH

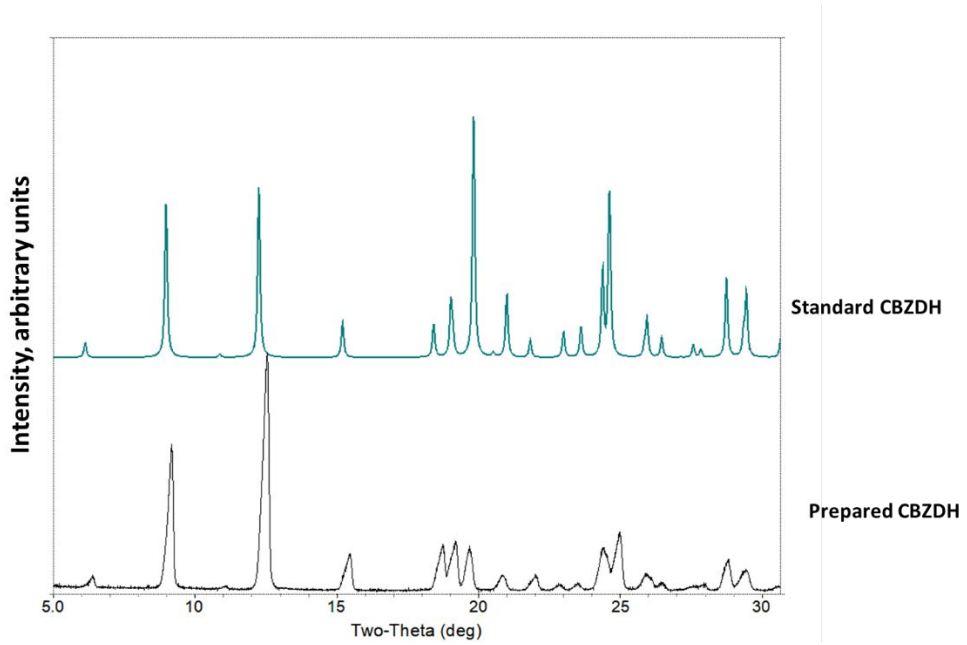


Figure S 4. XRD patterns of the prepared CBZDH plotted as an overlay with the standard pattern of CBZDH.

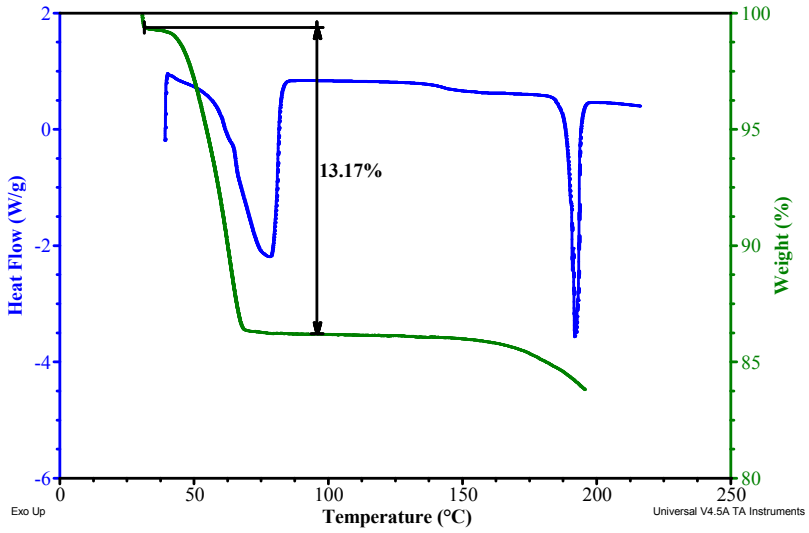


Figure S 5. DSC (blue curve) and TGA (green curve) heating curves of prepared CBZDH.

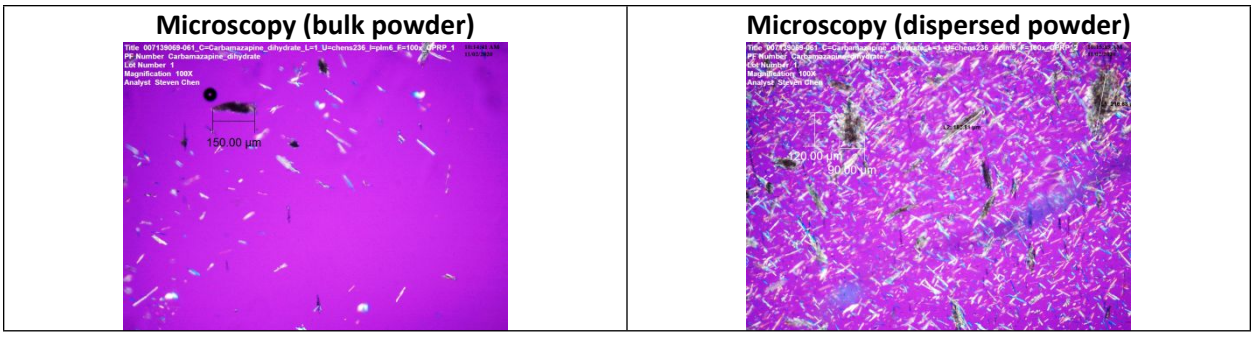
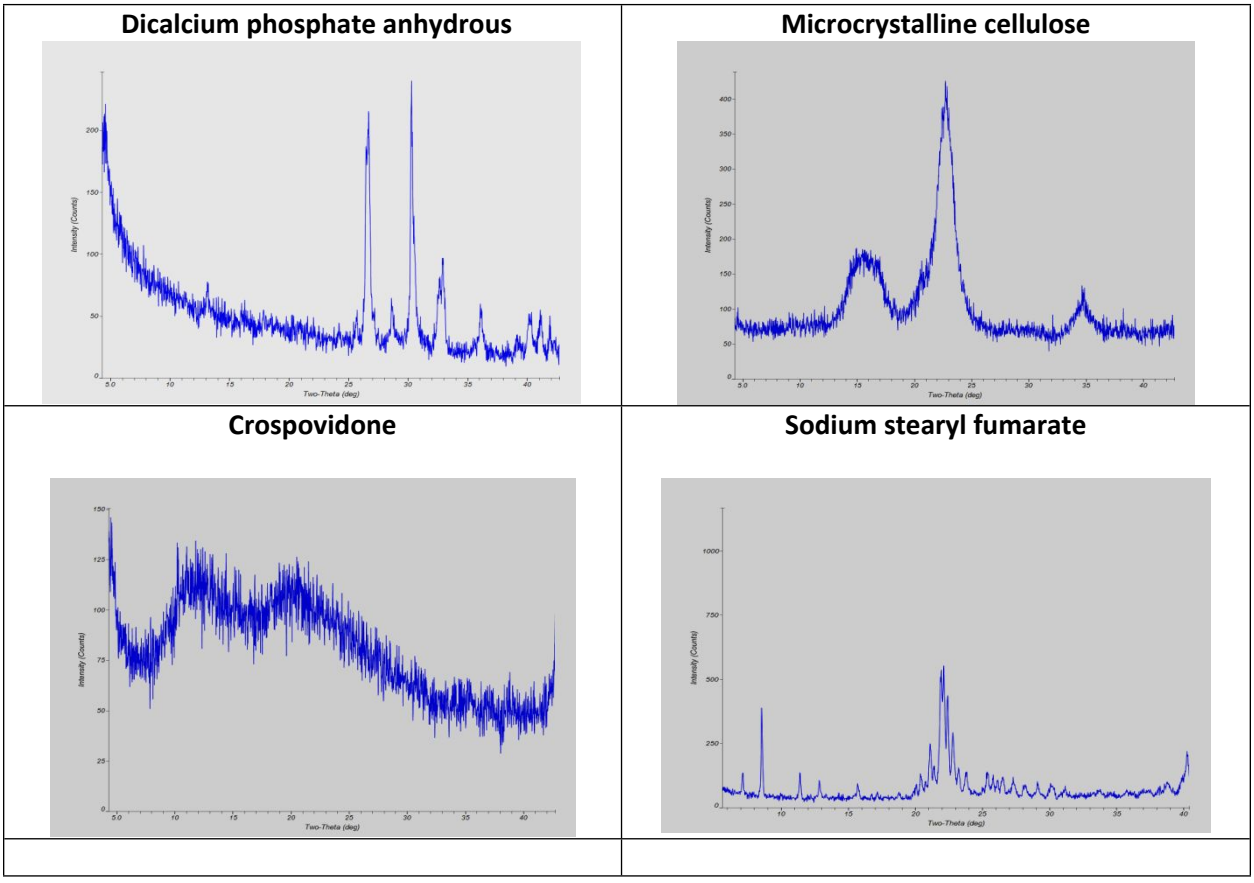


Figure S 6. Microscopy of the prepared CBZDH

Baseline characterization of excipients



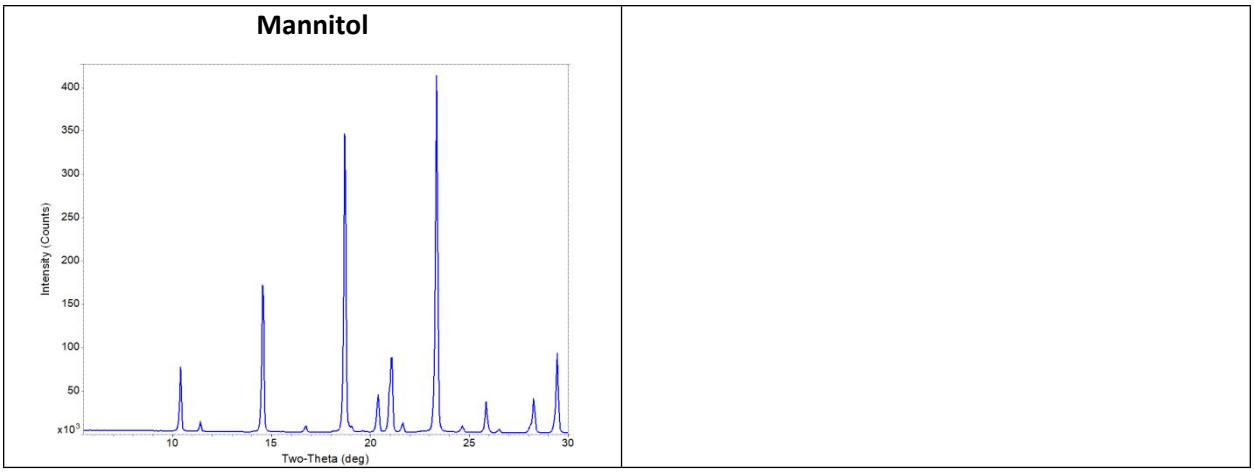
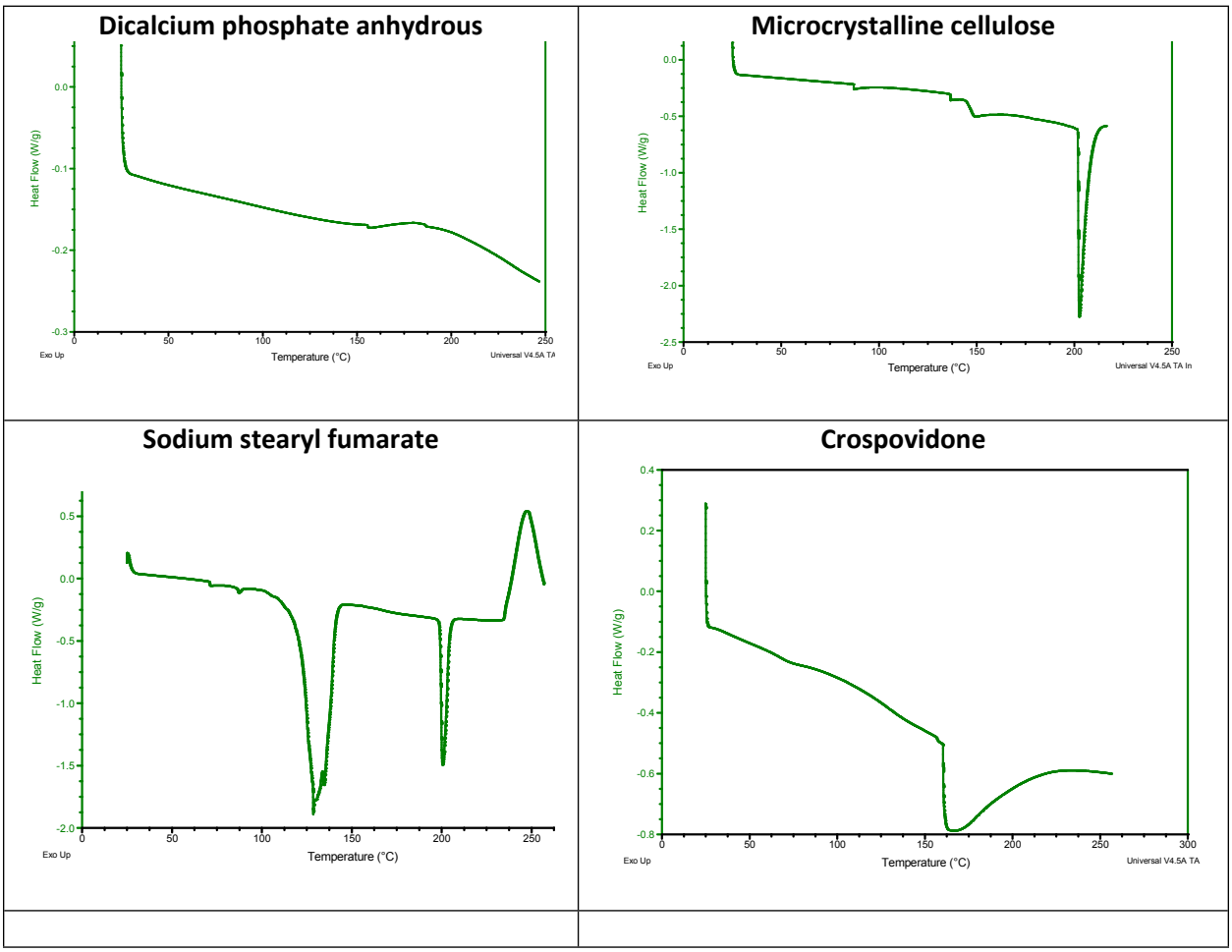


Figure S 7. XRD patterns of the individual excipients.



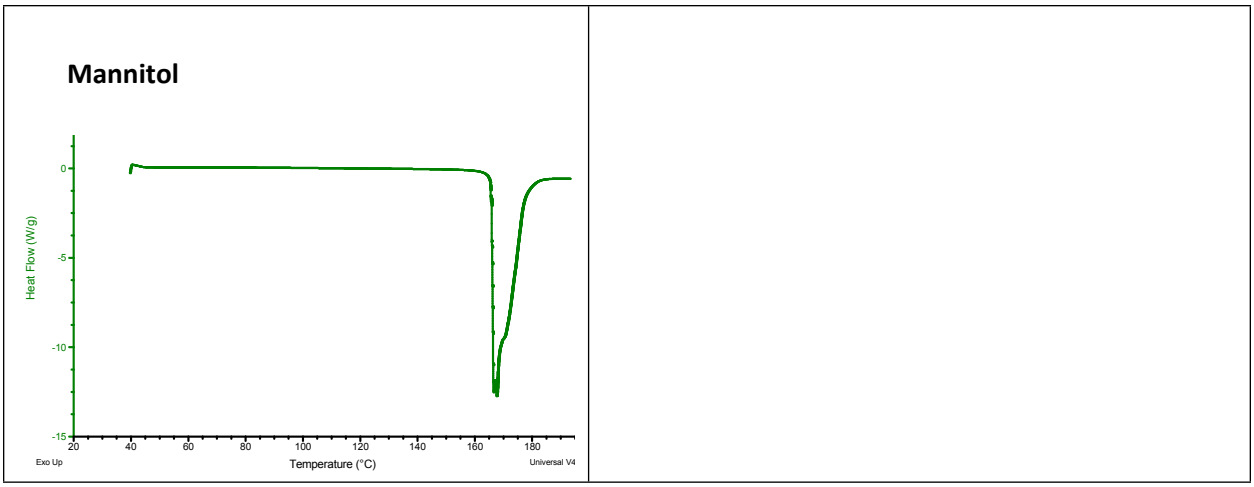


Figure S 8. DSC heating curves of individual excipients.

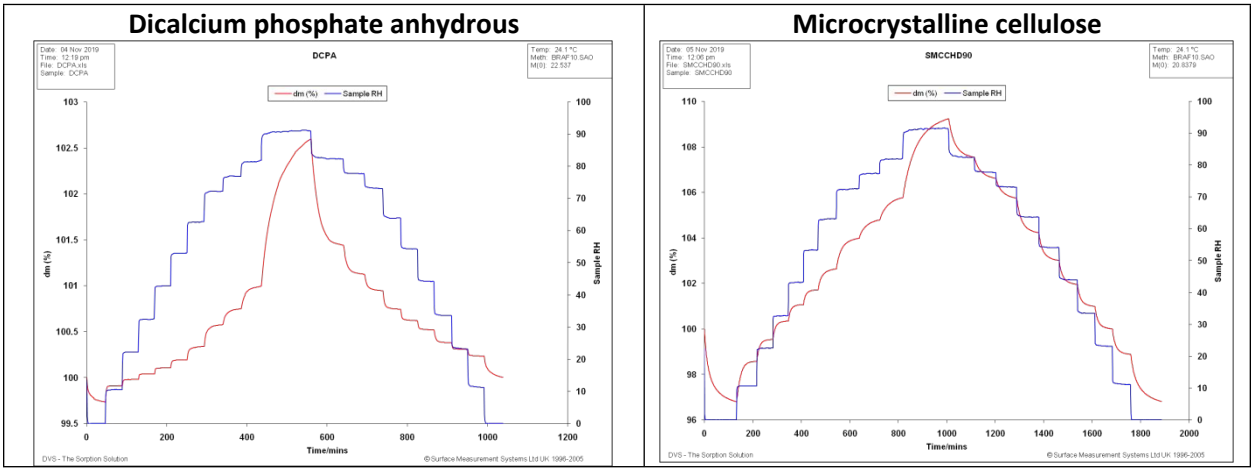


Figure S 9. Water sorption-desorption isotherms of dicalcium phosphate anhydrous and microcrystalline cellulose at 25 °C.

Methods used for baseline characterization of 'as received' API, prepared CBZDH and excipients

Differential scanning calorimetry (DSC)

Thermal analysis of powder samples was performed using a differential scanning calorimeter (Q2000 by TA Instruments) equipped with a refrigerated cooling accessory (RCS 90). The powder sample (2-5 mg) was hermetically sealed in an aluminum pan with a pinhole. Measurements were performed at a heating rate of 10 °C/min, from RT to 200 °C, using a nitrogen purge rate of 50 mL/min. The data were analyzed using Universal Analysis software version 4.5 (by TA Instruments).

Thermal gravimetric analysis (TGA)

The powder sample (2-5 mg) was placed in an aluminum pan and heated in a thermogravimetric analyzer (Q50 TGA by TA Instruments), under a dry nitrogen purge, from 25 to 200 or 250°C at 10 °C/min. The data were analyzed using Universal Analysis software version 4.5 (by TA Instruments).

Water content by Karl-Fischer titrimetry (KFT)

Accurately weighed quantity of the sample (10- 20 mg) was added to the titration cell, and the water content was determined coulometrically using a Karl Fischer titrimeter (DL36, Mettler Toledo, Columbus, OH). Data has been reported in %w/w of the powder.

Water Sorption and Desorption Analysis

The water sorption profiles of individual excipients were obtained using an automated water vapor sorption/desorption Analyzer (DVS-1000 Advantage, Surface Measurement Systems, Middlesex, U.K.). Approximately 20.0 mg of powder was placed in a quartz sample pan and equilibrated at 0% RH (25 °C) for 30 min under a nitrogen flow rate of 200 mL/min. The relative humidity (RH) was progressively increased from 0 to 90% RH, in increments of 10% RH and then decreased back from 90 to 0% RH in steps of 10% RH. At each RH, the attainment of equilibrium was assumed if the mass change was <0.005% in 10 min. The maximum hold time at each RH was not more than 2 h.

Determination of dead volume of the CMT and optimization of the sampling procedure

The dead volume of CMT was defined as the powder volume that could remain undisturbed even after starting the impeller. The dead volume was determined by adding small increments of powder blend and observing the powder movement using a camera. The dead volume corresponded to a powder weight of ~7-8 g. Accordingly, at every sampling point, first a 10 g aliquot was taken,

followed by another 2 g sample. The latter was used for the analysis, while the former was added back to the hopper. This ensured that the sample in the dead volume was not a part of the aliquot analyzed.

Identification of characteristic distinguishing peaks of CBZDH

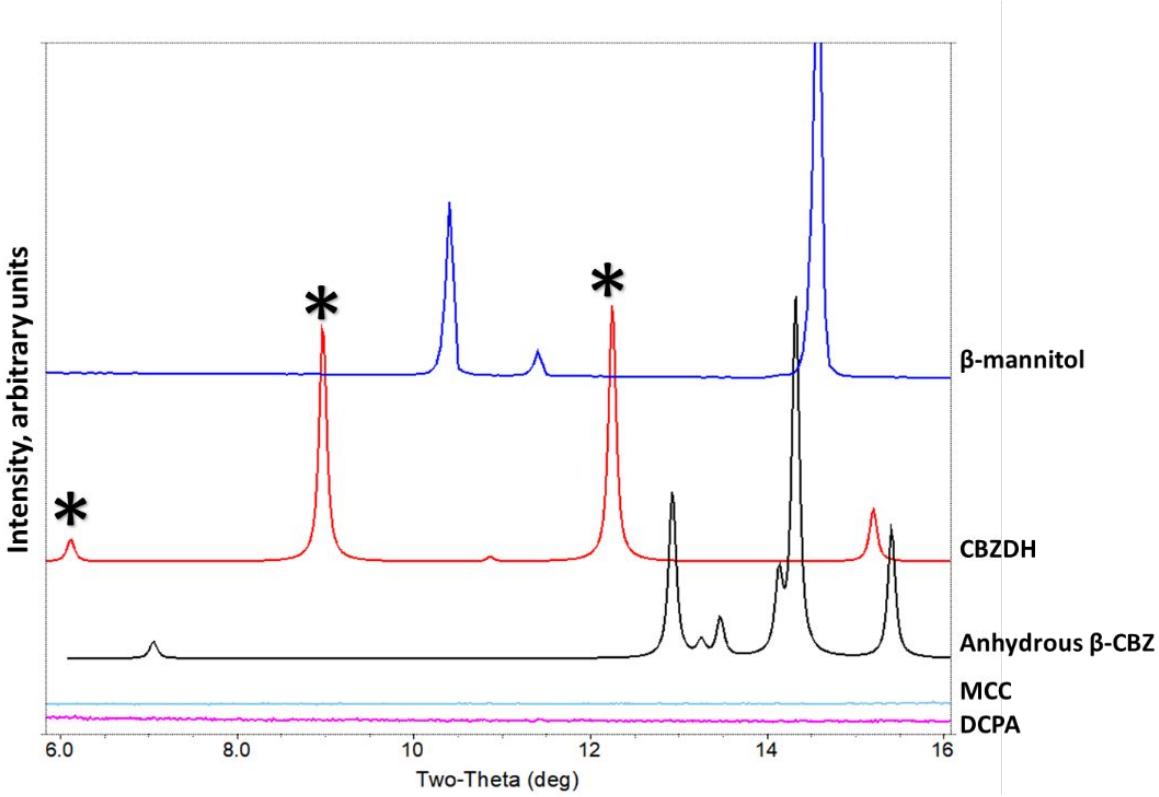


Figure S 10. XRD patterns of the major excipients with β-CBZ and CBZDH. '*' represents the characteristic peaks of CBZDH used for quantification of CBZDH.

Calculation of sorbed water content (Figure 8)

The sorbed water content of the sample was calculated based on the dihydrate content (determined using XRD) and water content (measured by KFT). The lattice water content at each sampling point was calculated based on the dihydrate content, using a value of 13.2% water content for 100% CBZDH. Accordingly, the initial lattice water content in the powder blends (containing 30% w/w CBZDH) was calculated to be 30% of 13.2 i.e., 3.96%. KFT measures the total water content,

i.e. sorbed + lattice water. Hence, subtraction of lattice water content from the total water content (determined by KFT) provides the sorbed water content (Figure 5) of the sample:

Sorbed water content = (water content measured by KFT) – (lattice water content based on the CBZDH content obtained using XRD)

FTIR analysis

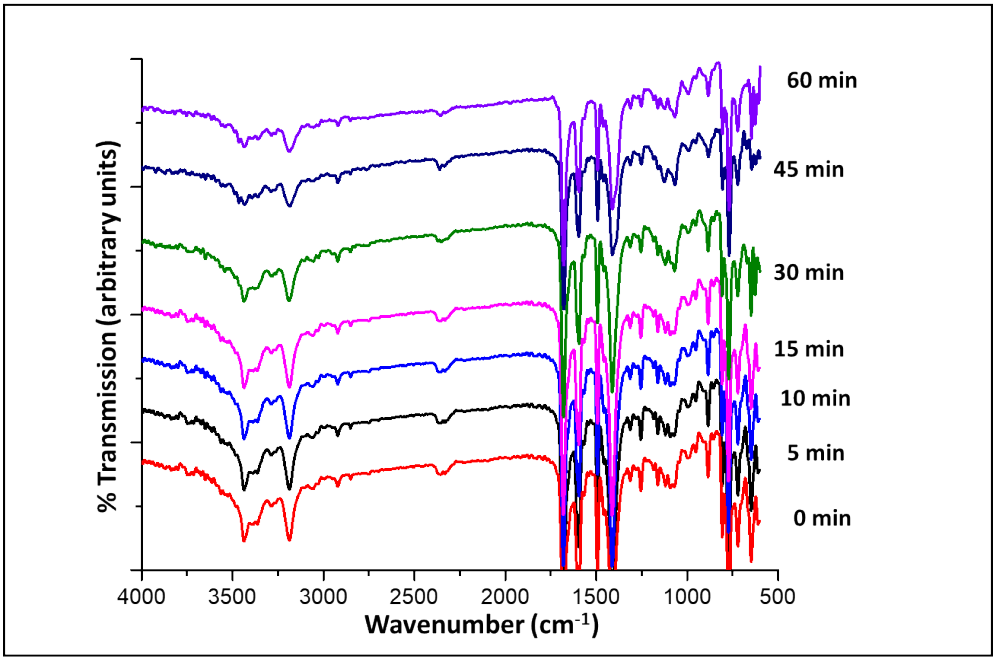


Figure S 11. FTIR spectra of the DCPA formulation as a function of blending time.

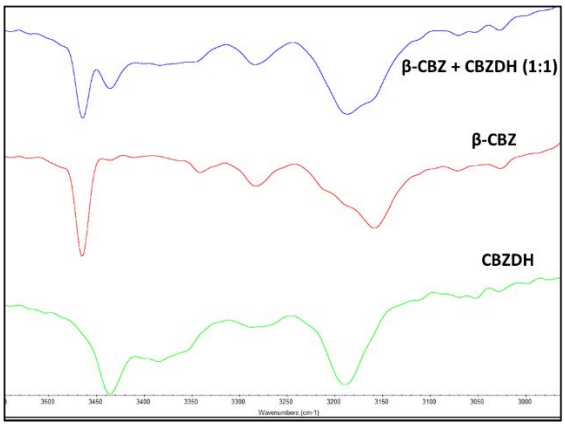


Figure S 12. FTIR spectra of the powder mixture of β-CBZ and CBZDH (1:1) shown as an overlay with β-CBZ and CBZDH.

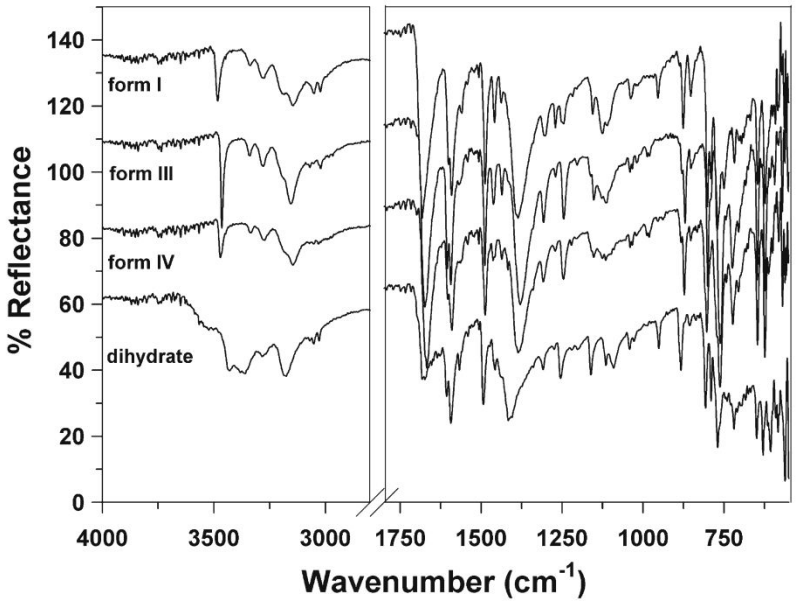


Figure S 13. ATR-FTIR spectra of CBZ forms I, III, IV, and the dihydrate. Reproduced from Kachrimanis and Griesser[1] copyright 2012 by permission from Springer Nature.

Effect of particle size on the dehydration behavior of CBZDH

A preliminary study was conducted to determine the effect of particle size of CBZDH on its dehydration behavior. API particles widely differing in size (a) < 149 µm (passing through #100 mesh) and (b) > 841 µm (retained on # 20 mesh) were exposed to 0% RH in an automated water sorption analyzer. The effect on dehydration kinetics was not substantial (Figure S14).

[1] Kachrimanis, K.; Griesser, U. J. Dehydration Kinetics and Crystal Water Dynamics of Carbamazepine Dihydrate. *Pharm. Res.* **2012**, *29* (4), 902–921

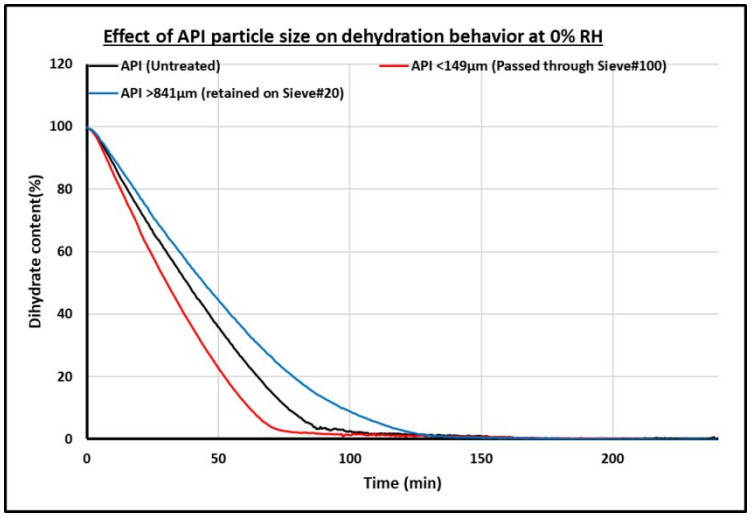


Figure S 14. Effect of particle size on the dehydration behavior of CBZDH upon exposure to 0% RH (25 °C) in a dynamic vapor sorption analyzer. API (Untreated) is the 'as is' API.