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Dissolution and precipitation studies of carbamazepine cocrystals with small scale assays

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PURPOSE

To better understand the dissolution properties and precipitation behaviour of carbamazepine cocrystals for the potential for oral administration based on a small scale dissolution assay.

METHODS

Carbamazepine cocrystals with saccharin and nicotinamide as coformers on a 1:1 molar ratio were prepared with the sonic slurry method whereby both API and coformer were introduced into an antisolvent and ultrasound applied. The acoustic cavitation induces nucleation and crystallization leading to the formation of well defined co-crystals.

Dissolution of the poorly soluble drug carbamazepine and the two cocrystals was studied with a small scale dissolution assay installed on a SiriusT3 instrument.
Detection and quantitation of carbamazepine was performed by in-situ UV-spectroscopy using a fibre-optic dip-probe. UV absorption data was converted to sample weight using previously determined (pH-dependent) molar extinction coefficients (also determined on the SiriusT3) to quantitate the amount of dissolved drug.

Two methodologies were used:

- **surface dissolution** of pressed pellet (3mm) in 20mL running for fixed times at four pH stages (pH1.8, pH3.9, pH5.4, pH7.3), and
- **powder dissolution** (4.1 mg) in 2mL at a constant pH (pH2).

RESULTS

Surface dissolution of pressed pellet

- Dissolution profiles from the pellets of the drug and of the cocrystals show that a higher amount of dissolved carbamazepine is observed for the saccharin cocrystal sample, but not for the nicotinamide cocrystal, compared to the carbamazepine sample

Powder dissolution

- The powder dissolution of all samples under constant pH reveals that carbamazepine initially dissolves much more slowly from the carbamazepine sample than from the cocrystal samples and also provides information regarding the precipitation and kinetic solubility of the samples.
- A drop in the concentration of carbamazepine from the carbamazepine sample is observed after 1.5h, probably due to the formation of a less soluble carbamazepine polymorph.
- Precipitation of carbamazepine dissolved from the carbamazepine-saccharin cocrystal takes place earlier than from the carbamazepine sample.
- Dissolution of the carbamazepine-nicotinamide cocrystal is also faster than carbamazepine, and the solution becomes heavily turbid as the carbamazepine precipitates rapidly from solution.

DISCUSSION

Poor solubility is a major issue for the development of new compounds. Several strategies have been developed in order to improve solubility with the ultimate goal of improving the absorption and bioavailability; the cocrystal strategy is one of them [1].

Carbamazepine was selected as the model compound. It has been classified as a BCS Class II compound with low aqueous solubility. Saccharin (SAC; sulphonic acid derivative pKa = 1.6]) and Nicotinamide (NIA; pKa 3.4) were the coformers selected for this study. Cocrystals were prepared using the sonic slurry method [2] whereby pre-dissolved API and coformer were introduced into an antisolvent in a jacketed vessel and ultrasound applied to induce nucleation and crystallization (Figure 1).

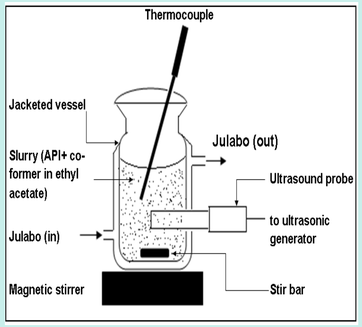


Figure 1: Sonic Slurry schematic [2].

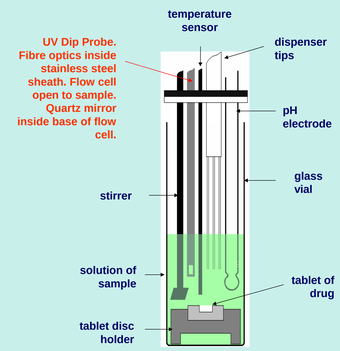
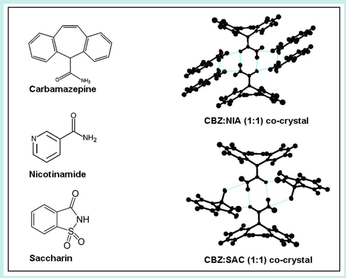


Figure 2: Small scale dissolution assay.

CBZ cocrystals (sonic slurry method)



Dissolution is often used to characterise the behaviour of materials. As cocrystals undergo solution-mediated phase transformation, their dissolution would represent many complex processes occurring simultaneously, such as the change of the solid form and of the surface area of the particles [3]. Therefore an appropriate dissolution design would provide important information relevant to their transformation and their absorption.

Small scale dissolution assays [4] can be used to illustrate the different behavior of the cocrystals (i) with respect to pressed pellet dissolution (Figure 2) as a function of pH and (ii) solubilization capacity and precipitation behaviour of powder samples at pH2.

Figure 3 shows pellet dissolution of the cocrystals compared to the API.

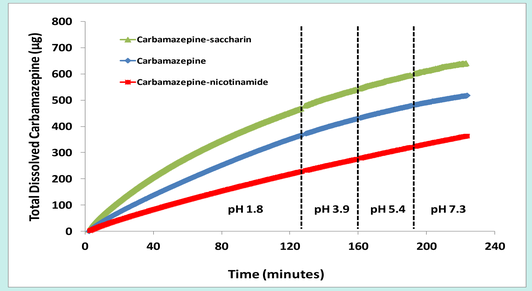


Figure 3: Dissolution of carbamazepine and cocrystal pressed pellets over four pH sectors.

Figures 4 and 5 show that powder dissolution of carbamazepine at pH 2 is faster than the pellet and reaches 185 µg/mL before precipitating after 90 minutes. The precipitation event probably represents transformation to a less soluble polymorph or hydrate. The powder of the CBZ-SAC cocrystal has a faster initial dissolution rate although the peak concentration is the same, (185 µg/mL) and precipitation is observed at a much earlier time point, i.e., ~12 minutes. Initial dissolution of the CBZ-NIA powder cocrystal is also rapid but precipitation occurs rapidly after ~4 minutes and the peak concentration only reaches 99 µg/mL.

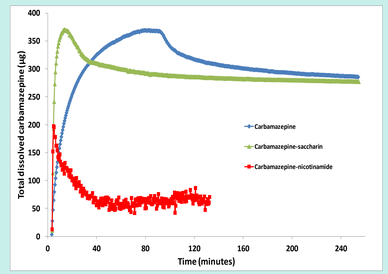


Figure 4: Dissolution of carbamazepine and cocrystal powders at pH2.

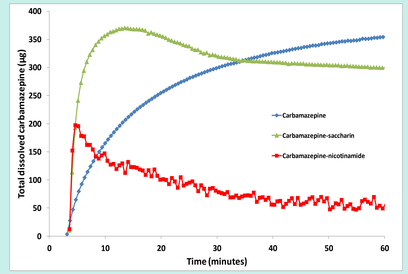


Figure5: Close-up of first 60 minutes.

CONCLUSION

The small scale dissolution assay provides useful information on the dissolution and the precipitation kinetics of carbamazepine from the cocrystal form. The type of coformer has a clear effect on the dissolution/precipitation behaviour of the carbamazepine cocrystals.

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