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Small Scale Assays For Studying Dissolution And Precipitation Of Pharmaceutical Cocrystals

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PURPOSE

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

METHODS

Indomethacin cocrystals with saccharin and nicotinamide as coformers 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 indomethacin and the two cocrystals was studied with a small scale dissolution assay installed on a SiriusT3 instrument.

Detection and quantitation of indomethacin 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** (2.6 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 the amount of indomethacin dissolved increases significantly when the pH of the dissolution medium rises above the pKa of indomethacin (4.06).
- A higher amount of dissolved indomethacin is observed for the two cocrystal samples compared to the indomethacin sample (Figures 3 and 4).
- The amount of indomethacin-nicotinamide cocrystal dissolved at the third stage (pH5.4) is lower than that observed for the indomethacin-saccharin cocrystal, but by the end of the fourth stage (pH7.3) there is a large increase in the total amount of indomethacin released from both cocrystals.

Powder dissolution

- The powder dissolution of all samples under constant pH (figures 5 and 6) reveals the solubilisation enhancement of the drug from the cocrystal samples, and also provides information regarding the precipitation and kinetic solubility of the samples.
- Dissolution of the indomethacin-saccharin cocrystal is faster than the indomethacin-nicotinamide cocrystal.
- The onset of precipitation of free indomethacin at pH2 occurs sooner for the indomethacin-saccharin cocrystal compared to the indomethacin-nicotinamide cocrystal.
- The final concentration of indomethacin is similar from both cocrystals suggesting that equilibrium solubility has been achieved.

DISCUSSION

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

Indomethacin 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 (NIC; pKa 3.5) were the coformers selected for this study. Cocrystals were prepared using the sonic slurry method [2] whereby pre-dissolved API and coformer are introduced into an antisolvent in a jacketed vessel and ultrasound applied to induce nucleation and crystallization (Figure 1).

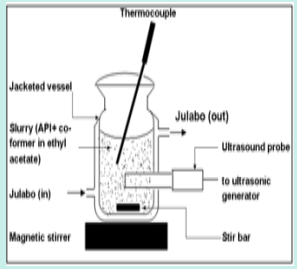


Figure 1: Sonic Slurry schematic.

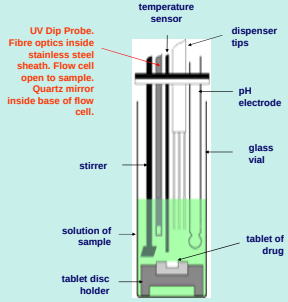
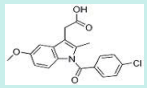
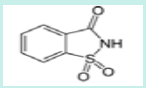


Figure 2: Small scale dissolution assay.

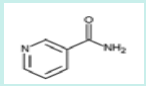
Indomethacin



Saccharin



Nicotinamide



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 behavior of powder samples at pH2.

Figures 3 and 4 show improved pellet dissolution of the cocrystals compared to the API but the greatest solubilisation occurs, in all cases, above the pKa of indomethacin when it becomes negatively charged.

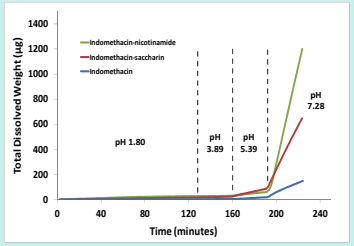


Figure 3: Dissolution of indomethacin and cocrystal pressed pellets over four pH sectors.

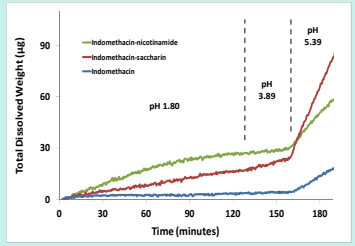


Figure 4: Close-up of first three pH sectors.

Figures 5 and 6 show that powder dissolution of indomethacin at pH 2 is very low for the duration of the assay reaching only ~4 µg in the 2mL volume and showing the poor solubility of the free form of the API. The powders of the cocrystals have improved dissolution performance but precipitation cannot be prevented as the solubility limit of indomethacin is soon exceeded as it is released from the cocrystal. Maximum solubilization from the saccharin cocrystal was ~17 µg/mL and from the nicotinamide cocrystal ~24 µg/mL.

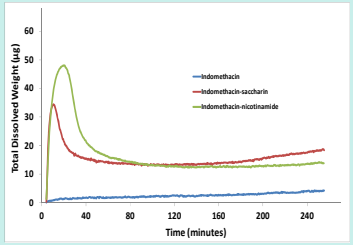


Figure 5: Dissolution of indomethacin and cocrystal powders at pH2.

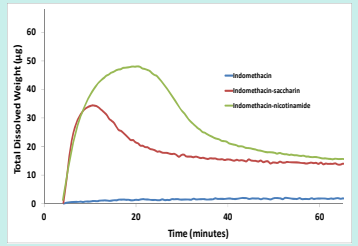


Figure 6: Close-up of first 60 minutes.

CONCLUSION

Improved dissolution and useful insights into precipitation kinetics of poorly soluble compounds from the cocrystal form can be revealed by the small scale dissolution assay. A clear difference in dissolution/precipitation behaviour can be observed based on the characteristics of the coformer used.

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Instrumentation
pKa, logP & logD,
Solubility, Supersaturation, Dissolution

CRO Services
PhysChem properties – pK_a, logP, logD, solubility, supersaturation, dissolution
Formulation Excipient Studies
Parenteral Solubilisation Studies
Solid state assays – XRPD, DSC, TGA, Raman
Surface Tension – CMC, TSA, K_{AW}

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