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Hydrochlorothiazide cocrystals: Structure, solubility and biphasic dissolution studies

Shanmukha Prasad Gopi[a], Somnath Ganguly[a], Gautam R. Desiraju[a]*,
Karl Box[b], John Comer[b], and Robert Taylor[b]
[a] Solid State and Structural Chemistry Unit, Indian Institute of Science, Bangalore, India
[b] Sirius Analytical Instruments Ltd, Forest Row, UK

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PURPOSE

To better understand the solubility and dissolution properties of a BCS class IV drug Hydrochlorothiazide (HCT). Being a class IV drug it has low solubility and permeability and hence exhibits poor oral absorption. The present study attempts at improving the physicochemical properties of the drug (solubility and biphasic dissolution) using a crystal engineering approach.

METHODS

Multi-component crystals of HCT were prepared with malonamide (MAM), picolinic acid (PIC), isonicotinic acid (INIC) and tetramethylpyrazine (TMP) using liquid-assisted grinding. The cocrystals were characterized using powder X-ray diffraction (PXRD), FT-IR spectroscopy and differential scanning calorimetry (DSC). Biphasic dissolution experiments were conducted on the Sirius inForm platform (Figure 1) and performed in 40 mL of an aqueous acetate-phosphate buffer adjusted to pH 6.5, with addition of 30 mL of decanol added as a lipid phase. Drug concentrations were determined by multi-wavelength UV-absorption spectroscopy using two in-situ fibre-optic UV probes and converting the UV absorption data to an absolute sample weight using molar extinction coefficients previously determined automatically on the inForm platform.

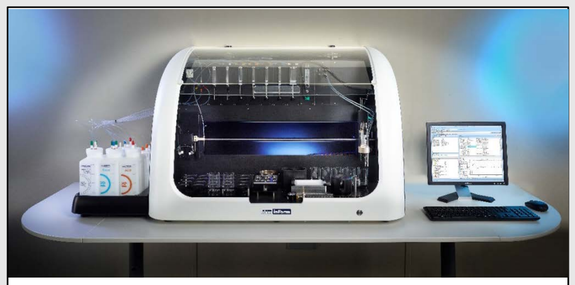
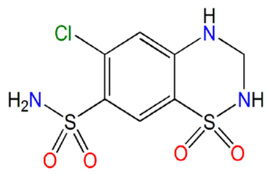


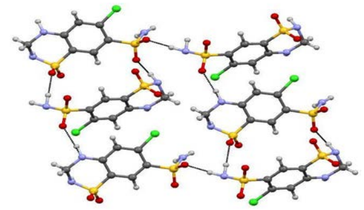
Figure 1: **Sirius inForm** platform used for biphasic dissolution testing

RESULTS

API AND API CRYSTAL STRUCTURES



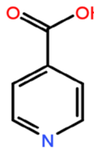
Hydrochlorothiazide (HCT)



HCT

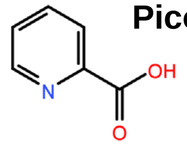
COFORMER STRUCTURES AND CRYSTAL STRUCTURES OF HCT COCRYSTALS

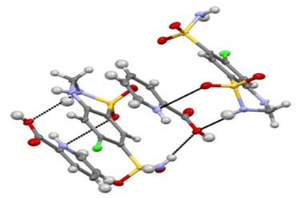
Isonicotinic acid (INIC)



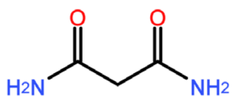
HCT + INIC

Picolinic acid (PIC)

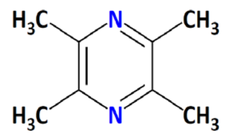




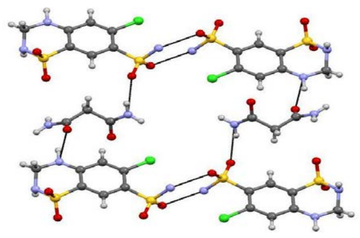
HCT + PIC



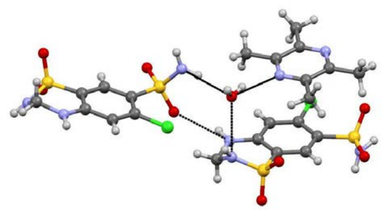
Malonamide (MAM)



Tetramethylpyrazine(TMP)



HCT + MAM



HCT + TMP

Single crystal X-ray diffraction (SCXRD) showed that the N–H···O sulfonamide catemer synthons found in the stable polymorph of pure HCT are replaced by drug-coformer heterosynthons in the cocrystals.

RESULTS

Solubility measurements in pH 7.4 buffer showed improvement in the solubility of all cocrystals compared to the API (figure 2) whilst biphasic dissolution studies showed highest partitioning by the API followed by HCT-MAM and HCT-TMP cocrystals both of which gave similar release and partition rates (figure 3). Highest solubility did not correlate to greatest lipid absorption whereas aqueous dissolution created a concentration gradient that did correlate to lipid uptake.

SOLUBILITY PROFILES

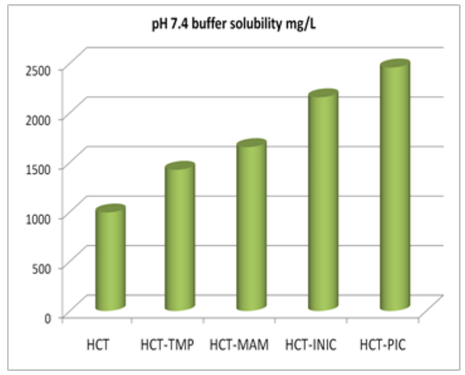


Figure 2: Solubility measurements on the API and cocrystals showing HCT-PIC and HCT-INIC with the largest increase in solubility at pH7.4.

BIPHASIC DISSOLUTION PROFILES

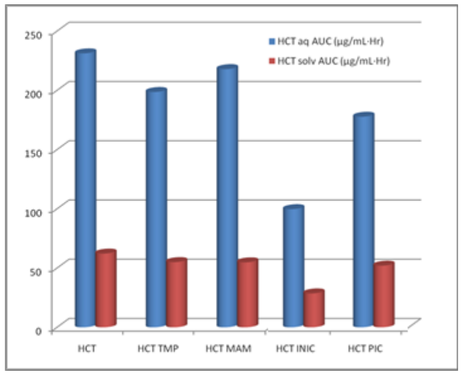


Figure 3: Biphasic dissolution results for the API and cocrystals at pH 6.5 showing area under the curves in the aqueous layer and the lipid layer. The overall extent of lipid partitioning correlates with the concentration dissolved in the aqueous compartment.

CONCLUSION

The physicochemical properties of HCT were altered by the formation of HCT-PIC, HCT-INIC, HCT-MAM and HCT-TMP cocrystals. The biphasic dissolution studies showed that the aqueous dissolution and partitioning into the non-polar phase were correlated; highest lipid absorption was observed when the rate and extent of dissolution in the aqueous phase was also highest.

REFERENCES

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