The Relationship between Crystal Structure and Physical/Chemical Properties in Pharmaceutical Materials

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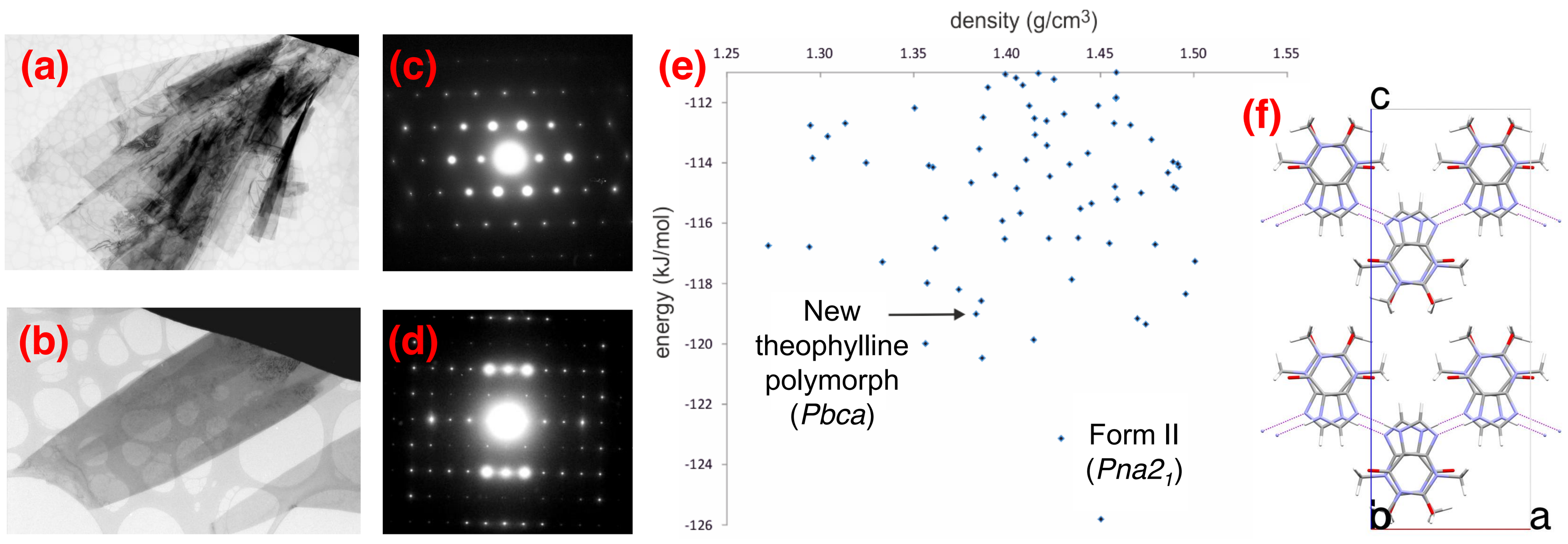
Introduction & crystal form characterisation

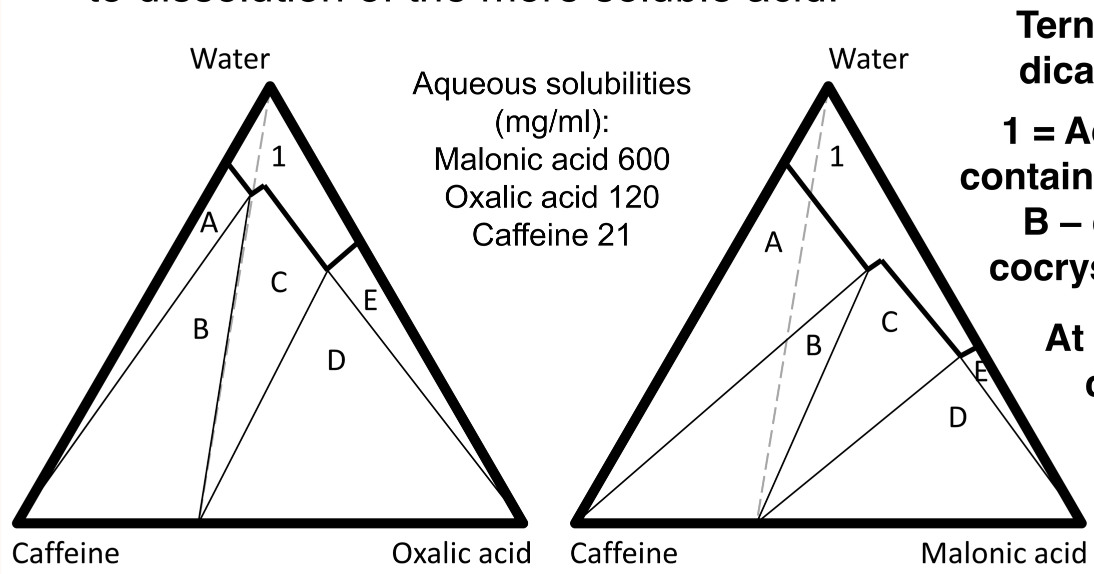
- Pharmaceutical compounds (APIs) can exist in a variety of different crystal forms such as polymorphs, salts and cocrystals. These forms have different solid state properties and will be absorbed at different rates in the body.
- Crystal forms selected for use in drug products must be sufficiently bioavailable to be effective, and also be stable (i.e. won't change form before taken by a patient).
- Analytical tools such as X-ray diffraction (XRD) / differential scanning calorimetry can distinguish and structurally characterise the different crystal forms of an API, allowing the physical stability of these forms to be studied, but have limitations.
- We have investigated the use of transmission electron microscopy (TEM) for pharmaceutical analysis, developing strategies for overcoming difficulties with sample preparation and beam damage, allowing the high resolution imaging and diffraction analysis possible with TEM to be utilised.[1]
- TEM was applied to the identification of the crystal form of individual crystallites, to mapping crystal habit to crystal structure and to the analysis of crystal defects.
- A new crystal structure determination method was developed for sub-micron sized crystals and mixtures of phases[2,3] (samples where XRD would not be applicable):



TEM analysis of a theophylline sample. (a) Triangular crystals of Form II make up the bulk of the sample. (b) Two lath shaped crystals were also identified. (c and d) Diffraction patterns from triangular crystals are consistent with Form II, those from laths are not. (e) The lath diffraction patterns were found to be consistent with a putative theophylline structure, (f), generated by crystal structure prediction.

Cocrystal stability

- Cocrystals are crystal forms comprised of two or more neutral molecules (coformers), and have different physical properties to the separate molecules.
- Cocrystals are particularly useful as the bioavailability of an API can be increased through cocrystallisation with a soluble coformer.[4]
- Cocrystallisation has also been used as a strategy to increase the stability of the APIs caffeine and theophylline to hydrate formation at high humidity: caffeine and theophylline cocrystals with oxalic acid were found to be kinetically stable even at 98%RH. Other dicarboxylic acid cocrystals partially dissociated.[5,6]
- We have subsequently investigated the stability of these cocrystals in the presence of water from a thermodynamic perspective.[7,8]
- 2:1 caffeine:oxalic acid is stable in water. Other cocrystals found to dissociate due to dissolution of the more soluble acid:

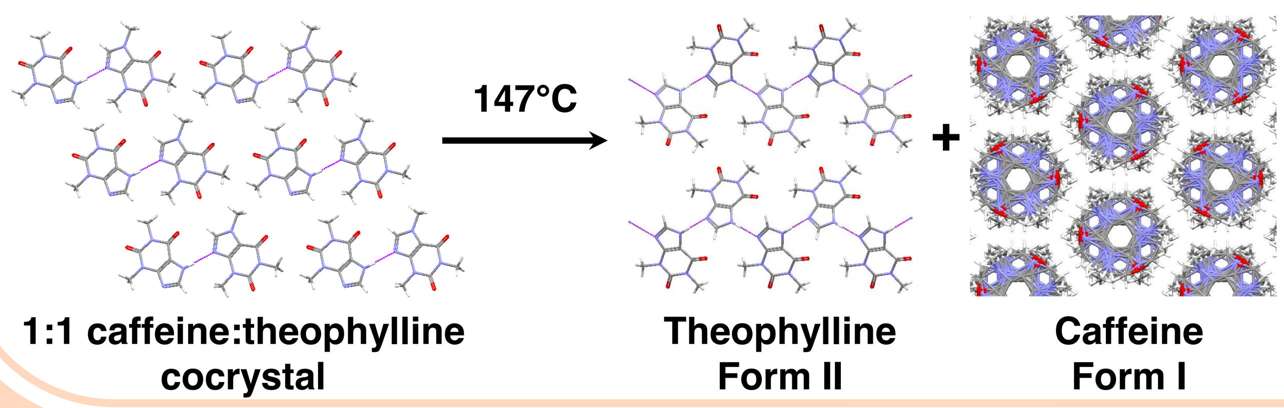


Ternary phase diagrams for caffeine: dicarboxylic acid cocrystal systems.

1 = Aqueous solution. All other regions contain solid phases: A – caffeine hydrate, B – caffeine hydrate + cocrystal, C – cocrystal, D – cocrystal + acid, E – acid.

At high humidity, water condenses on cocrystals resulting in the system compositions moving upwards along the dotted line. This causes the malonic acid cocrystal to dissociate.

- Importantly, cocrystals comprising an API + soluble coformer are prone to dissociation. Cocrystal dissociation on heating has also been investigated:[9]

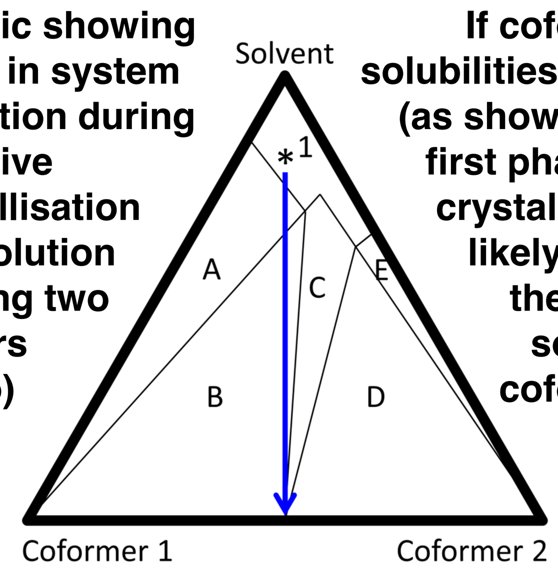


Cocrystal dissociation is driven by formation of an entropically favourable rotator phase of caffeine.

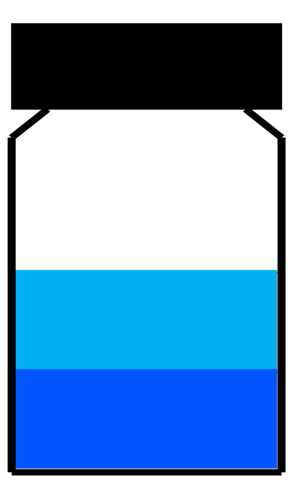
Cocrystallisation methods

- Batches of API are most commonly prepared by solution crystallisation.
- With cocrystals, however, solubility differences can lead to the coformers precipitating as separate phases rather than as a cocrystal (see figure below).
- As a result, the use of solution crystallisations for identifying cocrystal forming compounds, or for screening for cocrystal polymorphs, is problematic.[10]
- Cocrystallisation techniques that use less solvent, such as grinding or slurrying, are widely used to avoid issues with coformer solubility differences. Because the coformers used in these experiments are usually in a crystalline form, however, it is possible that they will persist due to self-seeding, rather than cocrystallising.
- We have developed two alternative approaches to cocrystallisation, freeze-drying and interfacial cocrystallisation, which offer advantages over other methods and have yielded novel polymorphic forms of cocrystals:[10,11]

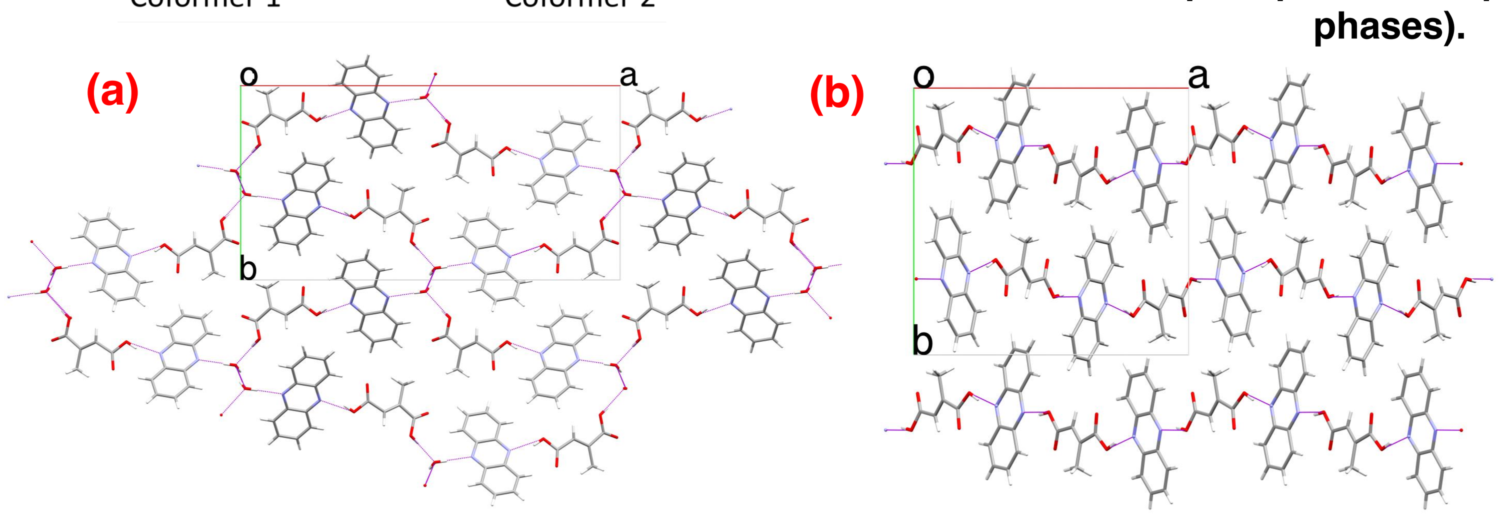
Schematic showing changes in system composition during evaporative cocrystallisation from a solution containing two coformers (1:1 ratio)



If coformer solubilities differ (as shown) the first phase to crystallise is likely to be the least soluble coformer



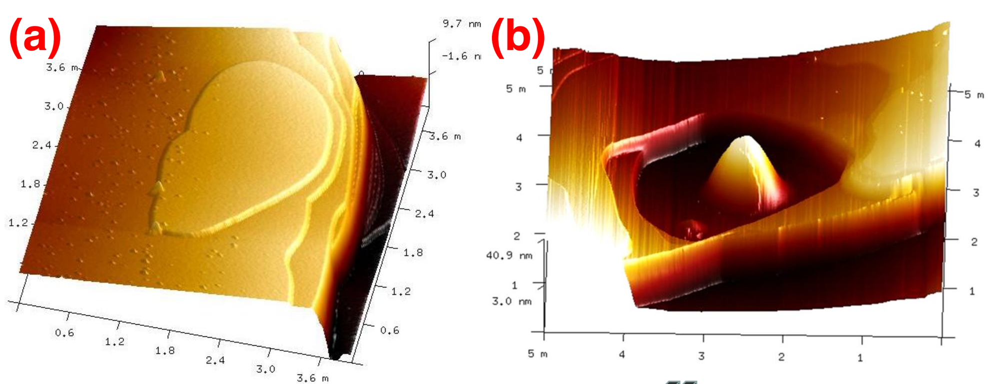
Interfacial cocrystallisation: A saturated solution of coformer 1 in a hydrophobic solvent is layered onto a saturated solution of coformer 2 in a solvent immiscible with the other. If a more stable, less soluble, cocrystal exists there will be a driving force for it to crystallise at the interface. (The coformers cannot precipitate as separate phases).



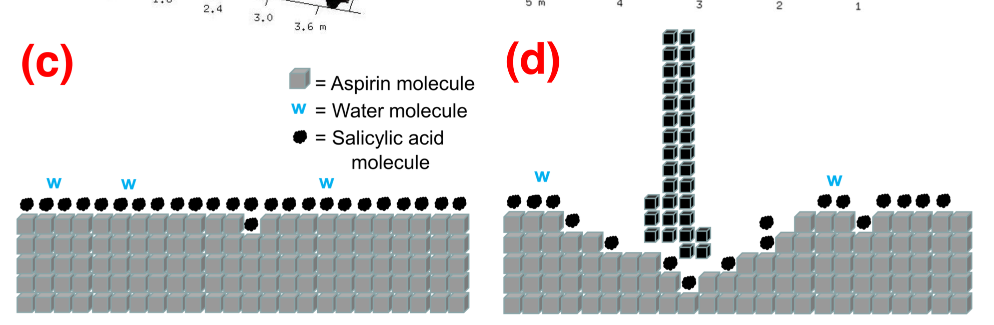
Interfacial cocrystallisation with phenazine and mesaconic acid yielded two new cocrystal forms: a monohydrate (a); and a stable anhydrous polymorph (b).

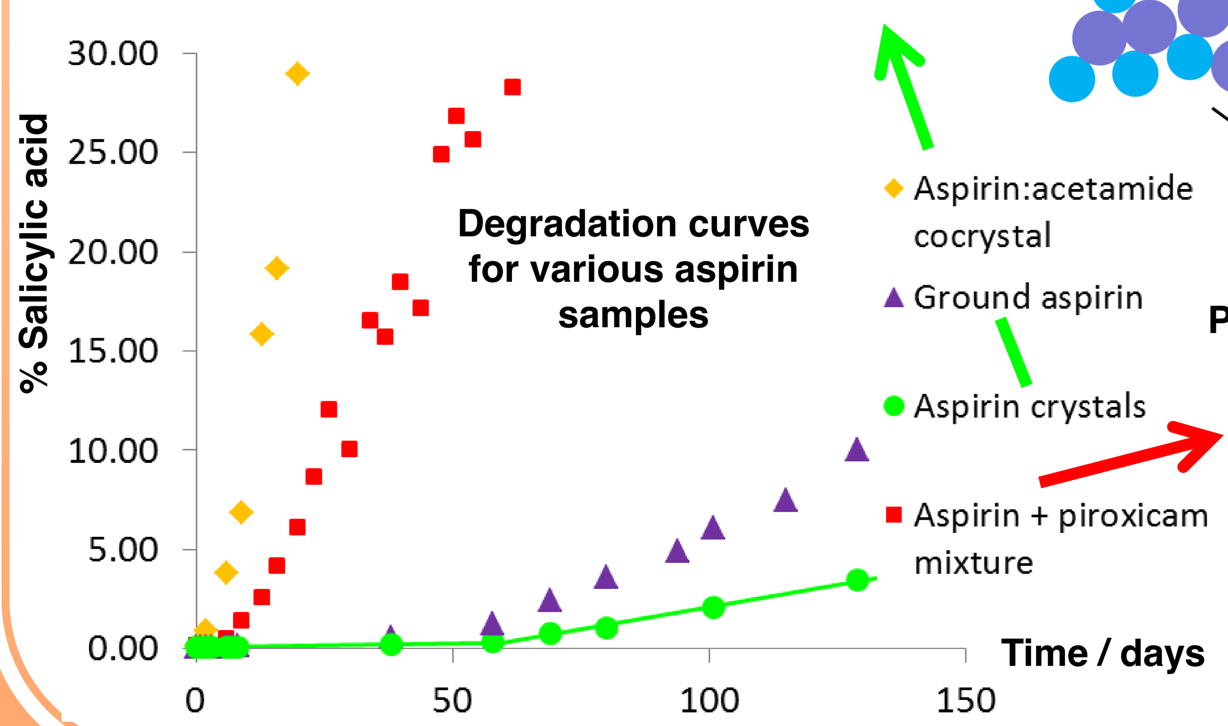
Chemical stability

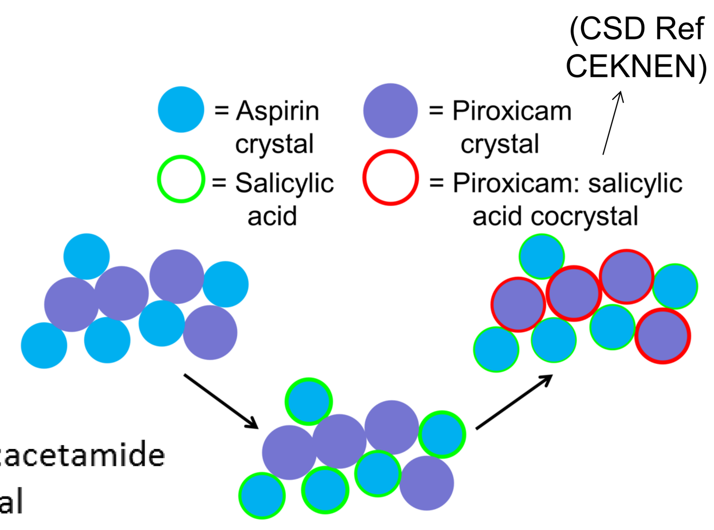
- Pharmaceutical compounds chemically degrade over time resulting in a reduced dose to patients and generation of potentially toxic bi-products.
- Batch-to-batch variability in solid state API degradation rates is common and shelf lives, given to protect patients, are often shorter than would be desired.
- There is, therefore, a need to better understand physical degradation processes.
- Aspirin: The rate of hydrolysis to salicylic acid in various aspirin crystal forms was measured at high humidity (96% RH) using HPLC. Changes occurring at crystal surfaces were monitored using atomic force microscopy (AFM):



AFM images of the aspirin (100) surface after (a) 2 days and (b) 39 days at 40°C/96%RH. Salicylic acid forms a protective layer by the 2 day time-point (c), but later crystallises (d) leading to an increase in the observed aspirin degradation rate.







Piroxicam cocrystallises with salicylic acid *in situ*. This removes the protective salicylic acid layer on aspirin particles resulting in high degradation rates.

References

(1) Eddleston M.D. et al, *J Pharm Sci*, **2010**, 99, 4072. (2+3) Eddleston M.D. et al, *Chem Eur J*, 2013, 19, 7874 & 7883 (4) McNamara D.P. et al, *Pharm Res*, **2006**, 23, 1888. (5+6) Trask A.V. et al, *Cryst Growth* Des, **2005**, 5, 1013 & *Int J Pharm*, **2006**, 320, 114. (7+8) Eddleston M.D. et al, *J Pharm Sci*, **2014**, Accepted. (9) Eddleston M.D. et al, *Chem Commun*, **2012**, 48, 8075. (10) Eddleston M.D. et al, *CrystEngComm*, **2013**, 15, 175. (11) Eddleston M.D. et al, *Cryst Growth Des*, **2013**, 13, 4599.