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 it is taken by a patient).
- Analytical tools such as X-ray diffraction (XRD) or 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.
- 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 (samples where XRD would not be applicable).

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.
- 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.
- We have subsequently investigated the stability of these cocrystals in the presence of water from a thermodynamic perspective.
- 2:1 caffeine:oxalic acid is stable in water. Other cocrystals found to dissociate due to the presence of the more soluble acid.

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.
- 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.

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).

References