

1 What are Pharmaceutical Cocrystals?

Pharmaceutical cocrystals are multi-component systems formed between an active pharmaceutical ingredient (API) and another cocrystal former¹. The components are held together by non-covalent interactions such as hydrogen bonds. Co-crystals offer the ability to optimize key physical properties of an API whilst retaining its biochemical or molecular activity as there is no making or breaking of covalent bonds.



Improved mechanical stability
Caffeine:Oxalic acid²

The coexistence of two API's
Piracetam:Genticic acid³

2 How are they made?

Typically cocrystals are prepared by slow solvent evaporation, a method that is only viable if compatible solubility in a given solvent exists between the components comprising the potential cocrystal.

Other screening methods that avoid the dependence on solubility have recently been considered, with increased popularity: these include 'grinding', 'slurring'⁴ and co-crystallisation from the melt (hot stage microscopy)⁵ has proved to be an excellent means of achieving the latter).

3 Sample analysis

The analytical problem is to distinguish cocrystals where both components are present in each crystal from mixed crystals where each crystal contains a single component. There are a number of techniques available to analyze a given sample for cocrystals.

The obvious approach is to interrogate a sample using single or powder X-ray diffraction, but the former method is only viable if a crystal of adequate quality and size is available while the latter requires a generous amount of sample. However, given the fact that cocrystals generally involve the formation of hydrogen bonds that are different from those associated with the individual components themselves, then a spectroscopic technique offers a quick and easy approach that is not so sample dependent.

4 Spectroscopic application

Initially, infrared spectroscopy was used to assess cocrystal formation. Where a cocrystal was formed, invariably there would be a shift in the OH and NH frequency. However, the spectra were often broad and generally fairly complex due to many more active modes inherently associated with the infrared spectrum. Here IR and Raman spectra are compared both for typical cocrystals and also for isomers and polymorphs in order to illustrate their sensitivities to minor structural and conformational differences.

The relative simplicity of the Raman spectrum offers potentially much clearer and less ambiguous assessment of cocrystal formation.

5 Why use Raman spectroscopy?

Both Raman and IR spectroscopy give fundamental information about the molecular structure of materials. Although in most molecules all the bonds will give rise to both infrared and Raman bands, it is the asymmetric, dipolar bonds such as carbonyl and hydroxyl groups that tend to give rise to the strongest infrared absorption bands. The strongest Raman signals, however, come from the more symmetric structures such as aromatic rings or C=C, S-S bonds.

Raman spectroscopy has the practical advantage that little or no sample preparation is needed, which is probably the biggest reason for preferring Raman spectroscopy to alternatives. The grinding and pressure that may be needed to obtain suitable material for measuring an IR spectrum can cause changes in crystal structure, although this is relatively uncommon.

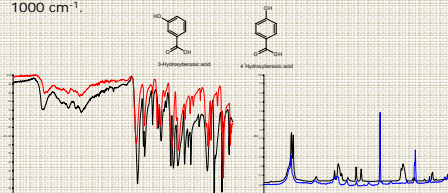
6 Experimental

The infrared spectra were collected at 4cm⁻¹ spectral resolution on a PerkinElmer Spectrum™ One FTIR spectrometer with an diamond ATR accessory. Raman data were also collected at 4cm⁻¹ spectral resolution using the PerkinElmer RamanStation™ 400 equipped with a 785nm excitation laser.



7 Hydroxybenzoic Acid

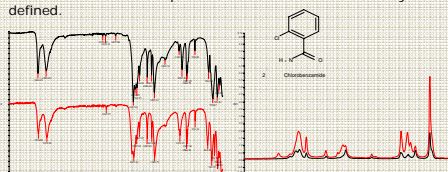
Hydroxybenzoic acid (3-OH) and (4-OH) are prolific cocrystal formers. Note differences in the spectra due to local symmetry. In the IR spectrum the key differences which are within the carbonyl and NH regions are not easily identifiable. However the Raman spectrum is simpler and sharper with a key difference at 1000 cm⁻¹.



8 Chlorobenzamide

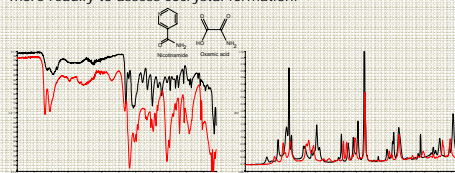
Another well known cofomer is 2-Chlorobenzamide, which has 2 polymorphic forms^{7,8}, of which form I converts to form II at high pressure (grinding).

The IR spectra of the two polymorphs are very similar with the main differences faintly displayed within the NH stretching region, whereas in the Raman spectra the differences are distinctly defined.



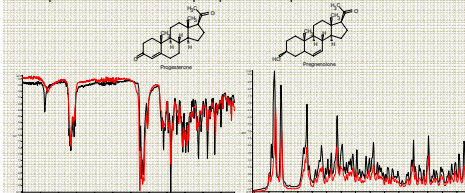
9 Nicotinamide: Oxamic acid cocrystal

Nicotinamide is another well used cocrystal former which also has a pharmaceutical relevance as its part of vitamin B group. The IR spectrum of the cocrystal of nicotinamide and oxamic acid compared to an arithmetic addition displays broad but discernibly different peaks. However, the corresponding Raman spectrum is significantly more different and as such could be used more readily to assess cocrystal formation.



10 Progesterone: Pregnenolone cocrystal

Both progesterone and pregnenolone are steroids associated with fundamental sex hormones and are the basis of many drugs of pharmaceutical interest. Both IR and Raman spectra are compared with an arithmetic addition of progesterone and pregnenolone pure forms. The IR spectra show characteristic peaks for the OH and carbonyl groups which themselves are subjected to significant and obvious shifts when the co-crystal is formed from its constituents. In comparison the Raman spectrum, though complicated shows a sharper pattern of peaks overall.



11 References and Acknowledgements

- Vishweshwar, P.; McMahon, J. A.; Bis, J. A.; Zaworotko, M. J. *J.Pharm.Sci.* 2006, 95, 499-516.
- Trask, A. V.; Motherwell, W. D. S.; Jones, W. *Cryst.Growth Des.* 2005, 5, 1013-1021.
- Vishweshwar, P.; McMahon, J. A.; Peterson, M. L.; Hickey, M. B.; Shattock, T. R.; Zaworotko, M. J. *Chem Commun.* 2005, 4601-4603
- Trask, A. V.; Jones, W. *Top.Curr.Chem.* 2005, 254, 41-70.
- Takata, N.; Shiraki, K.; Takano, R.; Hayashi, Y.; Terada, Y. *Crystall. screening of stanolone and mestanolone using slurry crystallization.* *Cryst. Growth Des.* 8, 3032-3037 (2008)
- Berry, D. J.; Seaton, C. C.; Clegg, W.; Harrington, R. W.; Coles, S. J.; Horton, P. N.; Hursthouse, M. B.; Storey, R.; Jones, W.; Friscic, T.; Blagden, N. *Cryst.Growth Des.* 2008, 8, 1697-1712.
- Kato Y, Takaki Y, Sakurai K. 1974. Polymorphism and Disordered Structures of o-Chlorobenzamide. *Acta Crystallogr., Sect. B*: 30, 2683-2758.
- Takaki Y, Kato, Y, Sakurai, K. 1975. An Analysis of Disordered Structures of o-Chlorobenzamide. *Acta Crystallogr., Sect. B*: 31, 2753-2758.

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12 Conclusion

Using a method where the spectrum of a cocrystal is compared to co-added spectra of cocrystal formers represents a quick and easy assessment of cocrystal formation (or otherwise!). Given the relative ease of sampling of Raman compared to infrared, coupled to the intrinsically sharper and simpler spectra obtained with Raman, we suggest that Raman would be the technique of choice for rapidly checking cocrystal formation.