

Polymorphism in Pharmaceuticals

During the last 5-10 years, the molecular solid state has gained recognition by the pharmaceutical industry for its role in drug manufacturing, stability, and activity. In addition, definition of the crystalline phase has become as important as molecular composition in patent protection.

The importance of this entire field has led to complete texts such as *'Solid-State Chemistry of Drugs'* (Byrn, Pfeiffer and Stowell, 1999) being devoted to this subject. Since the physical state can effect the pharmaceutical behaviour of drug substances, it is important to know what controls crystallisation, solid state reactions, phase stability, and solubility. There are numerous methods that have been used to measure the solid state composition of pharmaceuticals; these include x-ray diffraction, optical microscopy, thermal analysis, dissolution testing, particle size analysis, NMR, and infrared (IR) spectroscopy. Curiously Raman spectroscopy does not appear on this list as yet, because it has not seen such widespread use as an analytical tool in this closely regulated industry.

Raman spectroscopy can however, provide qualitative and quantitative information on polymorphy, with $1\mu\text{m}$ spatial resolution when necessary. The new generation in Raman technology, provides many advantages over the other techniques.

- Non contact, non-destructive analysis. Samples can even be examined in transparent glass or plastic containers.
- Microscopic samples as small as $1\mu\text{m}$ can be easily characterised with the Raman microprobe.
- Polymorphic and pseudo-polymorphic phases in microscopic samples can be mapped.
- Little or no sample preparation is required.

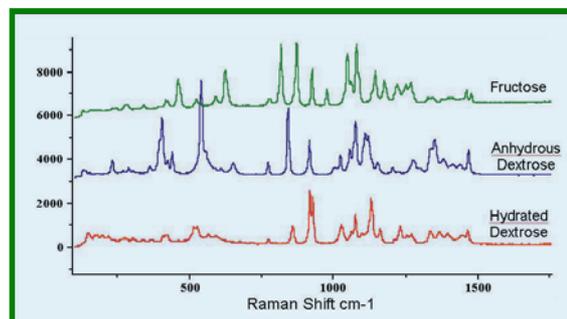
The lack of necessary sample preparation, and the ability to examine samples *in-situ* and in many types of transparent vial is an important advantage of Raman as a new characterisation tool. If we consider infrared (IR) spectroscopy,

which is the other widely used vibrational spectroscopy, we see that many container materials have limited transmission to the IR light. Furthermore, IR examination, often requires samples to be mixed with salts or nujol oils and pressed into pellets for examination. These procedures are time-consuming, and introduce additional chemical and physical variables; for instance, the pelletizing can create pressure-induced polymorphic transformation.

The sensitivity of the information provided by drug analysis within the pharmaceutical industry, means that little Raman data has been openly published. We present in this application note, spectra of organic crystals which may be used as non-commercially sensitive models to illustrate the potential of Raman spectroscopy in providing the useful characterisation of pharmaceutical formulations.

1. Fructose, anhydrous dextrose, and hydrated dextrose

These three compounds are obviously not active drugs, but they do bear a close similarity to many pharmaceutical compounds. Their spectra illustrate several points

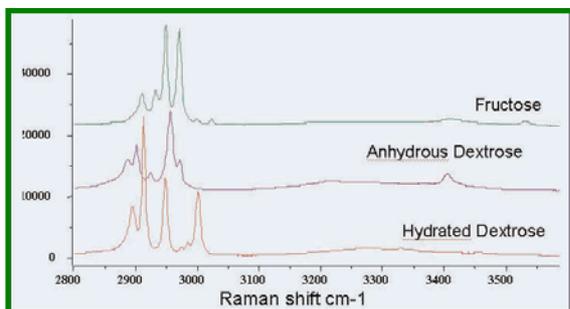


Fructose and anhydrous dextrose share the same chemical formula, but are different chemical isomers. Anhydrous and hydrous dextrose differ in the water of hydration in the crystal of the hydrous form - in the pharmaceutical nomenclature, it is a pseudo-polymorph. For clarity the spectra have been split into the fingerprint regions ($100\text{-}1750\text{cm}^{-1}$) and CH/OH regions ($2500\text{-}3700\text{cm}^{-1}$). Inspection of the spectra shows clear

differences between these species that would enable rapid identification of them. Such spectroscopic differences could easily be used to establish presence and indeed distribution of the different compounds.

2. Stearic acid

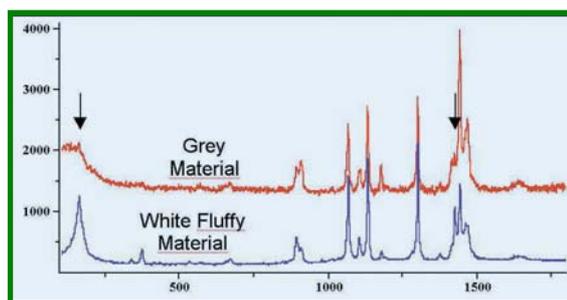
The spectra shown in the following figure were generated from material that had been dissolved in hexane, and then precipitated during evaporation. Two phases were observed with optical microscopy - a grey, fairly planar material, and a white 'fluffier' material of very fine crystals.



Although the spectra in the accompanying figure look fairly similar there are some observable differences. The bottom spectrum, recorded from the white phase, shows a well-defined feature at about 165 cm^{-1} , and differences in relative intensities in the 1400-1500 cm^{-1} region when compared to the second form. An explanation of the origin of these differences is that the grey material represents a less crystalline and more amorphous material than the bottom spectrum of the white fine crystals. Evidence for this is shown by the presence of the well-defined band at about 165 cm^{-1} which is consistent with a lattice vibration (only present in a crystalline phase), and also in the behaviour of the bands in the region of the CH_2 bending motion (1400-1500 cm^{-1}). The spectral differences in this region have a strong precedent in the comparison with the

behaviour of polyethylene where, crystallinity also effects the spectral features in this region. Systematic studies of polyethylene, which can have different states of crystallinity, indicate that when crystalline there is a fairly strong band at about 1420 cm^{-1} which is absent in the amorphous phase^{1,2}.

3. Summary



Simple Raman measurements of even 'off-the-shelf' organic materials illustrate that it is possible to differentiate between materials that differ by :

- stereo isomer,
- polymorphy,
- pseudo polymorphy (due to water of hydration).

The potential of analytical Raman instrumentation in qualifying pharmaceutical products in this area is only now beginning to be exploited.

1- G.R. Strobl and W. Hagedorn, Raman Spectroscopic Method for Determining the Crystallinity of Polyethylene, J. Polymer Sci.: Polymer Phys. Ed. **16**, 1181-1193 (1978)
 2- M. Glotin and L. Mandelkern, A Raman Spectroscopic Study of the Morphological Structure of the Polyethylenes, Colloid & Polymer Sci. **260**, 182-192 (1982)