

Raman Analysis of a Polymorph Within a Polymorph

It has long been known that some molecules with the same chemical formula can have different chemical structures. These different structures are called polymorphs. There are two ways in which different crystal structures can arise: Arrangement (or packing) polymorphism and conformational polymorphism. Pseudopolymorphs are crystalline structures that also incorporate solvent molecules and are therefore not chemically identical to the true polymorphs.

Arrangement polymorphism occurs when rigid molecules of the same conformation pack in different ways. The monoclinic and hexagonal forms of Glycine are examples of this type of polymorphism.

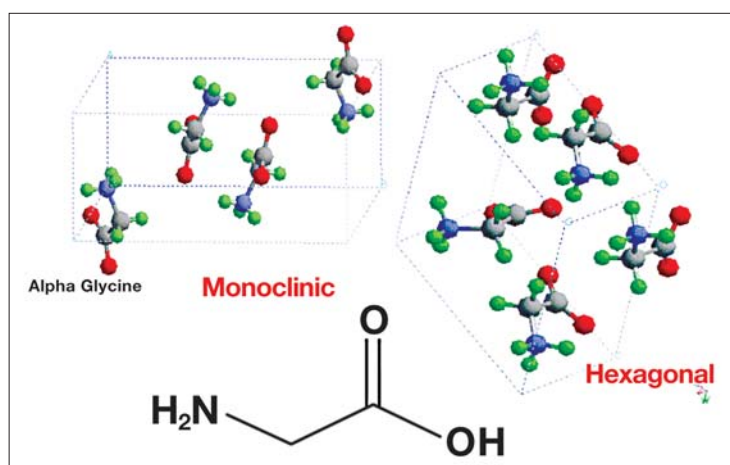


Figure 1. Different arrangement polymorphs of Glycine.

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Conformational polymorphism occurs when flexible molecules with different conformations pack in different ways. An example is the two forms of Spiperone.

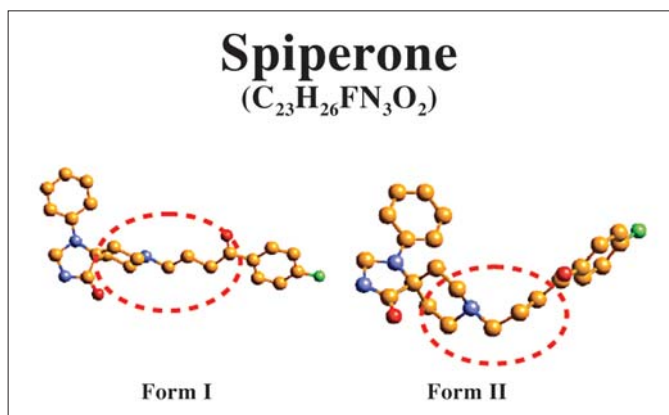


Figure 2. Different conformational polymorphs of Spiperone.

The differences in the crystalline structure of these polymorphs can affect the physicochemical parameters of the substance such as solubility, dissolution rate, density, hardness and shape. This in turn can impact on important pharmaceutical properties of these polymorphs such as bioavailability and stability of a drug as well as the formulation technology of the dosage form. The differences between the solid polymorphs are lost on melting and dissolution.

The formation of different polymorphs is a controllable process within formulation. Factors such as solvent of crystallization, rate of cooling and degree of supersaturation can affect the crystallographic form produced. Powder processing, especially pressure in the form of grinding or milling can also change the polymorphic form.

In the pharmaceutical industry it is therefore vital to manufacture the correct polymorphic form and to access its continued viability throughout its formulation, storage and subsequent usage. It is also of great commercial importance to pharmaceutical companies when filing patents for new products.

There are several recognized analytical techniques which are commonly used to analyze and differentiate between these polymorphic forms. Most commonly used techniques include X-Ray powder diffraction (XRD), thermal analysis techniques such as DSC and TGA, as well as vibrational spectroscopy (IR and Raman). Raman is recognized as being one of the most powerful and

simple techniques for polymorph analysis, although using a combination of techniques is sometimes advantageous. This application note indicates how Raman spectroscopy can be used in the study of an important polymorphic drug product.

Ranatadine Hydrochloride is one such polymorphic molecule that can exist in two distinct forms and several other pseudo-polymorphic forms. It is a histamine type 2 receptor antagonist used in the treatment of peptic ulcers. Form I of the drug was first prepared in 1977 and the first U.S. patent registration was in 1978. In 1980 Form II of the drug was discovered and in 1985 the patent for Form II was registered in the U.S. In 1984, GSK first marketed the drug as Zantac® (Figure 3) in the U.S. and by 1992 sales of Zantac® had reached \$3.44 billion. In 1995 and 2002 respectively, the original patents for Form I and Form II expired.

In addition to Zantac 75®, there are many other generic drugs based on Ranatadine HCl available for the treatment of peptic ulcers. All of these products are in the form of a coated tablet and the active Ranatadine is present in a high dosage. The coatings on these tablets are relatively thick and often pigmented. Visible images, acquired using the RamanStation™ video camera, showing the coating on Zantac 75® (left) and a generic tablet (right) are shown in Figure 4.



Figure 3. Zantac 75® relief tablets.



Figure 4. Surface of Zantac 75® relief and generic tablet.

Raman spectra from the core of these tablets

The Raman spectra from the core of a Zantac 75® tablet and the core of a generic Ranatadine tablet were measured using the PerkinElmer® RamanStation 400 instrument (Figure 5).



Figure 5. The sampling stage of the RamanStation 400.

The outer coating of the tablet was removed prior to analysis. The resulting spectra are shown in Figure 6 and are the result of a 1 minute accumulation time. They show a spectral range of 3200-100 cm^{-1} and have a spectral resolution of 4 cm^{-1} .

Although there will be a small contribution from minor excipients, these spectra are essentially the spectra of the Ranatadine HCl present in these tablets.

It is clear that these two tablets contain the different polymorphic forms of Ranatadine, with the Zantac 75® tablet containing Form II and the generic tablet containing Form I. The reason for this difference almost certainly lies in historical patent restrictions. Both forms have been tested to ensure they have the same effects on the human body.

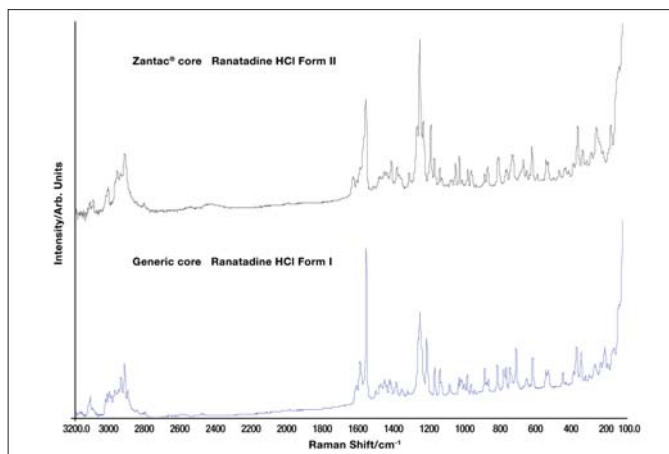


Figure 6. The different forms of Ranatadine HCl found in the two tablets.

To obtain the above spectra the coating was removed from the tablets. In many instances it is advantageous to be able to analyze the bulk product through a packaging material (glass, thin polymer, etc.) or through a coating. The RamanStation 400 is an ideal instrument for this type of analysis. By focusing on the surface of the coating of the samples and recording the spectrum, the resultant spectrum is a mixed spectrum with a major contribution from the coating and a secondary contribution from the bulk material. This spectrum from the generic tablet is shown in Figure 7. The major peaks below 650 cm^{-1} are from the coating. The contribution from the bulk material is shown in the much smaller peaks from 650-3200 cm^{-1} .

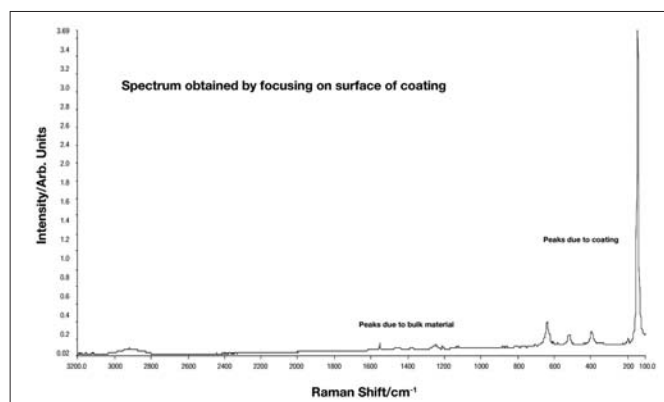


Figure 7. Spectrum obtained from tablet coating.

The automated x,y,z stage of the RamanStation 400 allows the analyst to collect spectra along a z-direction through the sample. A series of spectra can either be obtained at a user-defined depth interval to obtain a line scan through the coating or, more simply, a second spectrum can be obtained from deeper within the sample by moving the z position up 1 or 2 millimeters. This second spectrum for this same sample is shown in Figure 8 where it is compared to the surface coating spectrum.

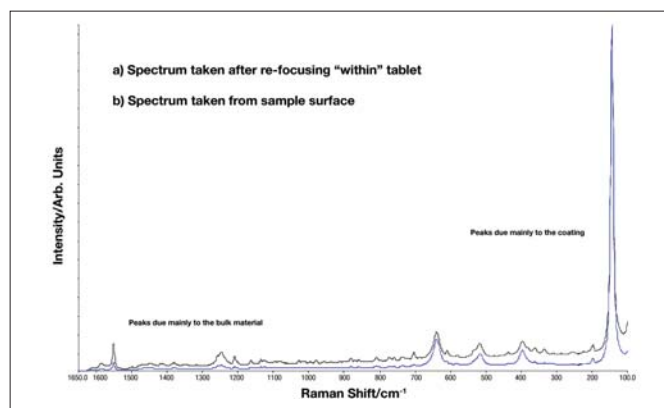


Figure 8. Comparison of spectra taken from different z-axis points.

The comparison of these spectra shows that although both spectra are dominated by the contribution from the coating, the relative contribution from the bulk material is considerably greater in this second spectrum. This difference in relative contributions allows the analyst to obtain spectra for both the coating and the bulk material by simply subtracting these spectra one from the other.

Subtracting the first spectrum from the second yields the pure spectrum of the bulk material. This 'difference' spectrum is shown in Figure 9 where it is compared with the authentic spectrum of the bulk material for the generic tablet. It is clear from this data that the bulk material can easily be identified as Ranatadine Form I by using this technique of scanning through the tablet coating.

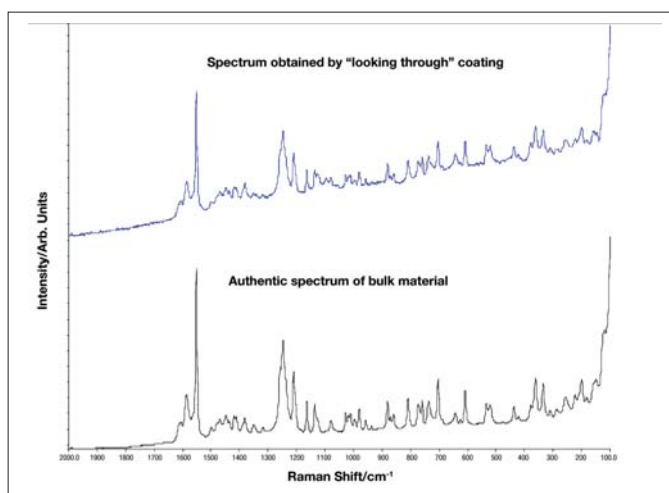


Figure 9. Comparison of 'difference' spectrum with authentic spectrum.

Similarly a subtraction of the second spectrum from the first spectrum yields a pure spectrum of the coating. This is shown in Figure 10.

This spectrum is also interesting since it is readily identified as Anatase which is a polymorph of Titanium Dioxide. Rutile is the other common polymorph of Titanium Dioxide (Figures 11 and 12).

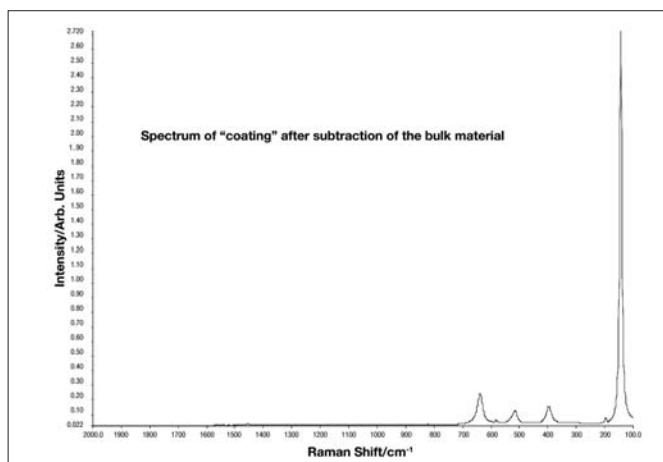


Figure 10. Spectrum of coating obtained by difference spectroscopy.

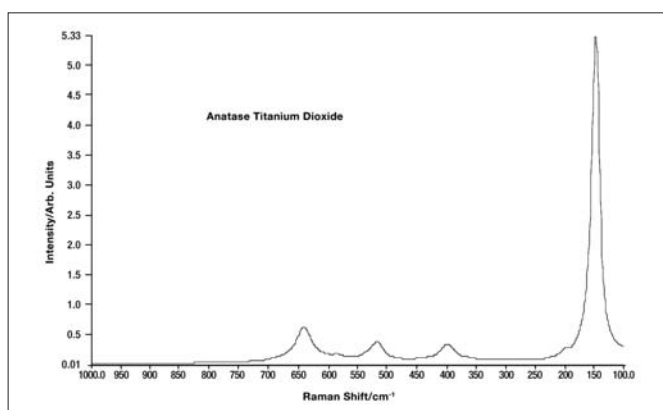


Figure 11. Reference spectrum of Titanium Dioxide (Anatase).

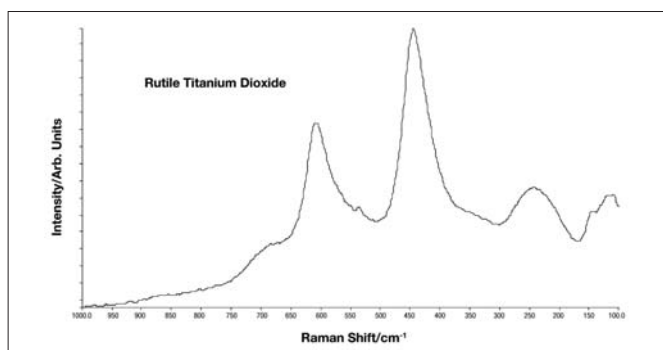


Figure 12. Reference spectrum of Titanium Dioxide (Rutile).

Therefore, what we have in this tablet is the polymorph, Ranatadine Form I, coated with another polymorph, Anatase.

A similar “z-axis” analysis of the Zantac 75® tablet followed by equivalent difference spectroscopy reveals that very good spectra of the Ranatadine Form II can be obtained through the coating and that the coating is the same as for the generic tablet, namely, Anatase (Figure 13).

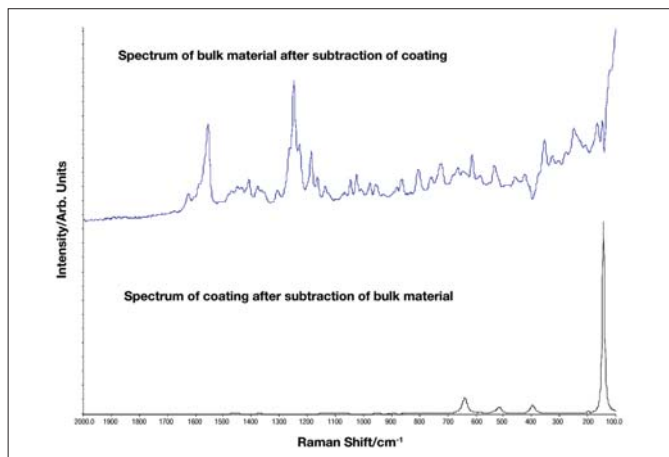


Figure 13. Spectra of bulk material (Form II) and coating (Anatase) by z-axis analysis through Zantac 75® tablet.

Conclusions

This study confirms that Raman spectroscopy is an ideal method for the analysis and identification of both organic and inorganic polymorphs.

Raman spectroscopy combines:

1. The high specificity of mid-IR allowing for small and sometimes subtle spectral differences to be detected and used to differentiate between polymorphic species.
2. The extended wavenumber range down to 95 cm^{-1} ensures that any spectral variation below 600 cm^{-1} can be routinely detected. This extended wavenumber range may not be available in many mid-IR spectrometers or may be an expensive option.

3. The amount of sample preparation to obtain a Raman spectrum is either nil or minimal. This ensures that there is no danger of inadvertently converting one polymorphic form into another during analysis. This is not always the case for mid-IR spectroscopy where, in the case of KBr disks or ATR measurements, the sample can be subjected to significant pressure with the danger of polymorphic conversion.

The RamanStation 400 features the following advantages for polymorphic analysis:

1. Very straightforward sample preparation and instrument use with no specialist requirement for setting-up the instrument or collecting the spectra.
2. Class 1 laser product (same as an FT-IR spectrometer) and therefore can be used in a general analytical laboratory.
3. Full range spectra (3500-95 cm^{-1}) with high spectral resolution combined with high sensitivity ensure that small differences anywhere within the spectra are easily detected.
4. Multisampler stage allows multiple samples to be analyzed automatically.
5. Intelligent x,y,z control of the stage allows the analyst to perform z-axis analyses through the surface of the sample. In the case of coated tablets, this enables the identification of both the coating material and the bulk material without having to compromise the integrity of the sample.
6. For those laboratories that require 21-CFR compliance, there is a version of the Raman Spectrum™ software which meets these requirements.

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