The Use of FT-Raman Spectroscopy in the Study of Formulated Pharmaceuticals

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KEY WORDS

DRIFTS
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INTRODUCTION

This note examines the advantages that the Fourier transform Raman (FT-Raman) technique offers pharmaceutical studies. It discusses the collection of spectra from formulated pharmaceuticals and draws comparisons between FT-Raman and Fourier transformation infrared (FT-IR) absorption measurements.

In 1986, Hirschfeld and Chase proved the FT technique of data collection was viable for Raman spectroscopy in the near-infrared (NIR) range. The ensuing commercial development of FT-Raman spectrometers using NIR lasers, has benefited many industries and research fields, including pharmaceuticals.

Raman spectroscopy has been used in pharmaceutical studies for many years. This is because compounds used in the pharmaceutical industry frequently exhibit strong Raman spectra, creating fast, high-quality data collection. Before the advent of FT-Raman spectroscopy with NIR excitation, Raman measurements were made with conventional scanning monochromator systems, using excitation lasers with emission in the visible region of the spectrum. The problem with this approach was that the dispersive spectrometer's visible lasers often excite not only the Raman scattering, but also fluorescence. This occurs in a large number of real-world samples. Because of the weak nature of the Raman signal, even moderate fluorescence can swamp any Raman data, preventing useful data collection.

By measuring FT-Raman spectra in the NIR range, many of these problems are avoided. The FT technique of data collection is well established due to its use of IR absorption components. The interferometer allows greater optical throughput than a conventional scanning monochromator, and it samples light more efficiently (It looks at all frequencies of light simultaneously, rather than one frequency at a time). Most importantly, FT-Raman avoids exciting fluorescence in almost all samples, making it a usable technique for general research and analysis, rather than for only a small number of spectra-emitting samples. Only with the advent of FT-Raman spectroscopy are laboratories considering Raman to be a routine, practical tool.

Pharmaceutical samples generally give excellent Raman spectra, even when diluted with carriers. Commercial drugs are often used in small doses and compounded in an inert matrix that allows them to be packed into tablet form. This provides a slow, controlled release of the drug in the body.

The intensity of Raman spectra obtained from different compounds can vary by a factor of 1000:1. This is unique to Raman spectroscopy (in FT-IR, all compounds have a similar overall absorption), accounting for high-quality spectra recorded from drugs even in low concentrations. In general, the spectra generated by drug compounds are stronger than those generated from carrier compounds.

Raman spectra are generally unaffected by highly polar bonds, such as C=0, 0-H, C-CI and amides, which produce very broad features in FT-IR and obscure other useful information. The generally narrow, uncluttered bands of Raman make the spectra ideal for subtraction, quantitative analysis and library referencing.

Several publications featuring FT-Raman for pharmaceutical studies have already been printed. Notable among these are Neville and Shurvell's study of antidepressants and related compounds[1], and the study by Nielson of anticancer agents[2]. Tudor's study of the controlled release of systems[3] involves the absorption of aqueous materials into the tablet. FT-Raman produces clear spectra while this analysis is unattractive with FT-IR (even using techniques such as diffuse reflectance or photoacoustic) due to water's strong IR absorption.

Raman has, in many cases, proven to be more sensitive to the detection of different polymorphs than FT-IR. Raman has been used to quantitatively analyze different polymorphs in several drug systems. Examples of this include the analysis of cimetidine[4] and the investigation of R69[5] – a drug used for the treatment of heart disease.

Most analytical and research laboratories are already familiar with FT-IR spectroscopy. Data from Raman spectroscopy is complementary to that from FT-IR spectroscopy in the sense that, while both give information on the vibrational structure of a molecule, most vibrational modes do not give rise to strong bands in both FT-IR and Raman spectra. Rather, bands which are weak or completely inactive in the IR tend to give strong Raman bands and vice versa. A full picture of the vibrational structure is achieved by examining both spectra. Thus Raman may be viewed as "another clue" in chemical analysis or as being useful in situations where the bands of interest are not active in the IR. *Note: IR is useful for the analysis of strongly polar bonds while Raman is more useful for the analysis of nonpolar or symmetrical bonds.*

Raman also has several practical advantages over IR. Raman spectra are recorded in the NIR or visible regions where glass is transparent. This means that holders for Raman samples are readily available. In fact, many samples can be studied directly through their laboratory bottles. Special cells for

studying in situ reaction kinetics, heated samples or any number of other applications may be constructed easily and cheaply. Any analyst with experience working with the materials available for use with FT-IR spectroscopy will quickly appreciate this benefit!

Of particular benefit to pharmaceutical chemists is the fact that Raman spectroscopy is, in general, a nondestructive technique which requires no sample preparation. While several methods have been developed for minimizing the sampling problems associated with FT-IR, they normally involve time-consuming sample preparation or the use of accessories. The ability of Raman to analyze samples in their natural state not only saves on valuable laboratory time, but makes in situ studies considerably easier and preserves the integrity of the data collected. These advantages will be illustrated in the examples given here.

RESULTS

In the examples discussed in this section, the samples were chosen from simple, readily available drug systems. All of the samples were purchased from a local pharmacy.

Our first example uses a paracetamol tablet as a sample. Tableted formulations of this kind normally make it difficult to obtain high-quality, FT-IR absorption spectra – direct transmission measurements on the sample in its raw form would obviously be hopeless. Many laboratories equipped with FT-IR already use Diffuse Reflectance Infrared Transform Spectroscopy (DRIFTS) accessories for this sample type. We used the Thermo Spectra-Tech DRIFT collector for this analysis. Using this accessory it is still necessary to perform significant sample preparation before a useful spectrum can be obtained.

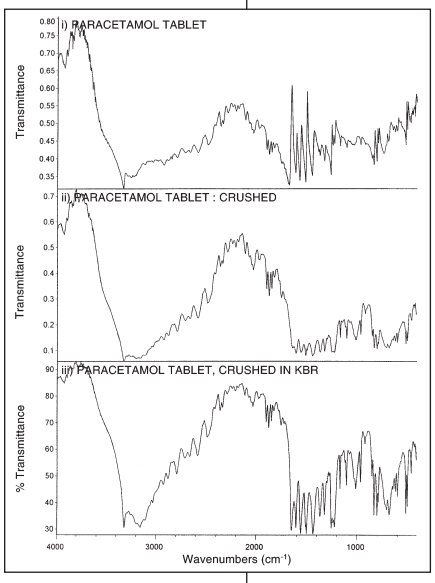

Figure 1: DRIFT FT-IR spectra of i) Paracetamol in solid tablet form, ii) Crushed paracetamol tablet, iii) Crushed paracetamol tablet, diluted with KBR

The three DRIFT FT-IR spectra represented in units of transmission in Figure 1 show stages in the preparation of the tablet – solid tablet, crushed tablet and crushed tablet diluted in KBr. In the spectra measured from the tablet directly, the only nondestructive method, the dominant features are caused by specular reflectance. This involves light reflected from the sample's surface with very little interaction with the sample itself. The amount of specular reflectance is reduced if the tablet is ground and further reduced on dilution with KBr. The best dilution factor must be determined for each sample but a general guide is 1-05% sample by weight. These same spectra are represented in the Kubelka Munk transform in Figure 2. Spectra were run at 4 cm^{-1} resolution and in approximately one minute of data accumulation.

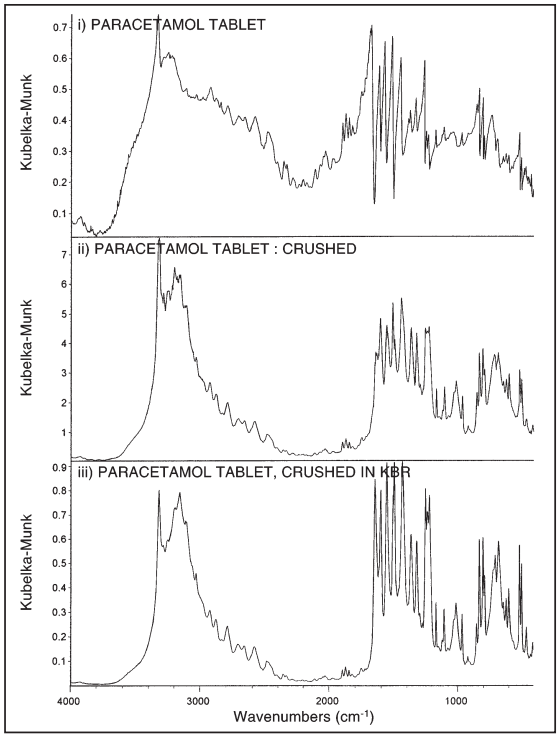

Figure 2: Kubelka Munk transformation of DRIFT FT-IR spectra of i) Paracetamol in solid tablet form, ii) Crushed paracetamol tablet, iii) Crushed paracetamol tablet, diluted with KBr

By contrast, the FT-Raman spectrum of the paracetamol tablet can be measured by placing the sample directly in the sample compartment. The variety of sample holders available makes this job simple. Raman data may be acquired with *no sample preparation* – this not only saves time but also means that Raman is free from the variations in preparation which often affect FT-IR spectra. The FT-Raman technique is *nondestructive*, allowing further tests to be performed after the Raman analysis.

The FT-Raman data is compared with the best of the DRIFTS spectra in Figure 3. The spectrum was accumulated for approximately one minute, using 800 mW of laser power and 4 cm^{-1} resolution. The spectrum is extremely high quality, the bands are narrow and distinct, and the structure of the active ingredient (paracetamol) dominates the spectrum. It should be noted that, unlike the FT-IR spectra, the FT-Raman spectrum contains no broad features which could mask the other bands present. This is particularly evident in the C-H stretching region of the spectrum, where the bands are strong and distinct in the Raman

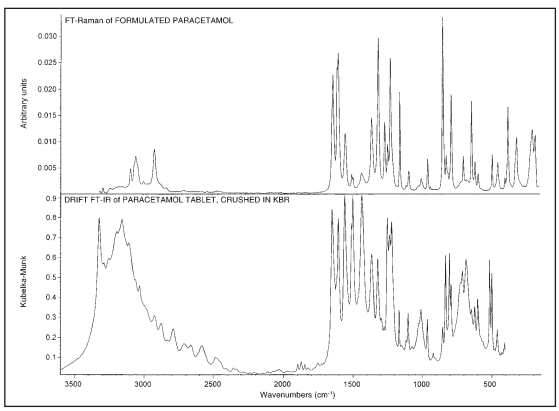

Figure 3: FT-Raman and "best" DRIFT spectra of formulated paracetamol

spectrum and almost completely masked in the DRIFT spectrum. This comparison also demonstrates that the FT-Raman technique is capable of producing constant reliable spectra, where the features of the DRIFT spectra are clearly dependent on the exact process of sample preparation which occurs.

Figure 4 shows FT-Raman and DRIFT FT-IR spectra of paracetamol formulated as a soluble tablet. Both of these spectra are dominated by the paracetamol and are, therefore, almost identical to the spectra shown in Figure 3.

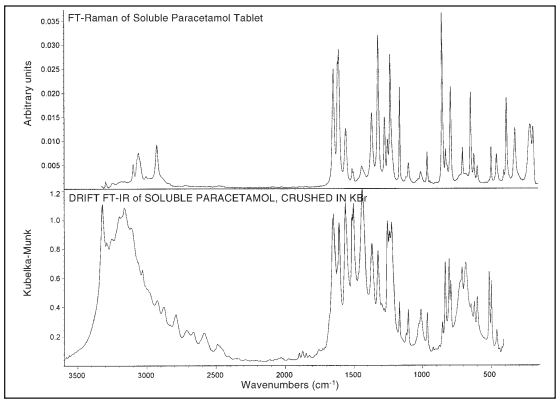

Figure 4: FT-Raman and "best" DRIFT spectra from formulation of soluble paracetamol

It is seldom the case that different formulations of a drug will immediately give identical spectra in this way. More frequently – especially with absorption data – other components will have their own distinct spectra, capable of masking the information of interest. To illustrate this, spectra of a painkiller were run in the form of an effervescent powder. Each sachet of this sample contained 500 mg paracetamol with metoclopramide (equivalent to 5 mg of the anhydrous substance). This light powder

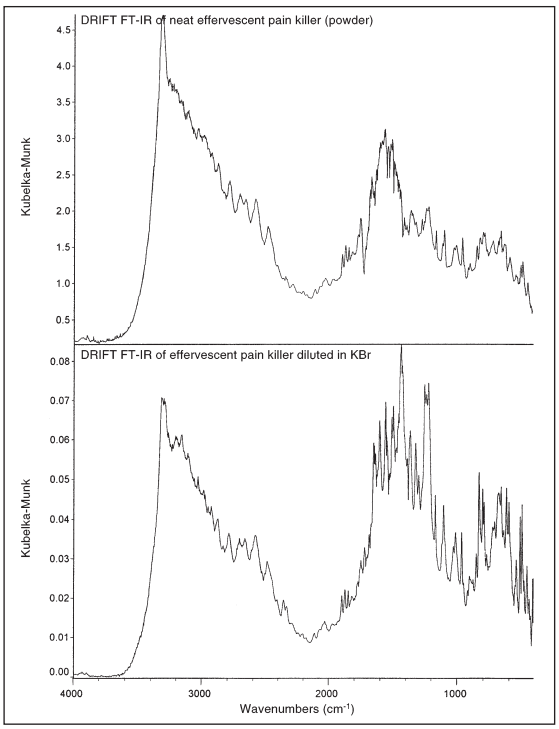

Figure 5: DRIFT FT-IR (after Kubelka-Munk transform) of a paracetamol based pain killer formulated as an effervescent powder, i) measured as neat powder, and ii) diluted with KBr

was difficult to pack tightly in the DRIFT "cup". As a result of this, and given that several other ingredients were included in the formulation, the DRIFT spectra shown in Figure 5 are not of particularly high quality and would be rather difficult to interpret. Again, several broad features in the spectrum mask potentially useful information.

The Raman data shown in Figure 6 is considerably clearer than the DRIFT results. Although strong bands are visible in the spectrum, they are sharp and independent from those of the paracetamol spectrum. Comparison with the paracetamol spectrum from Figure 3 shows how simply Raman bands from the different compounds can be identified – the same cannot be said of the DRIFT data.

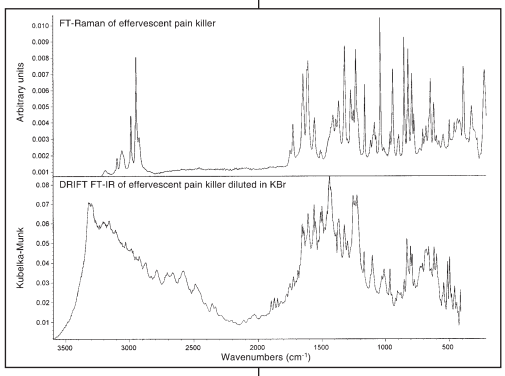

Figure 6: FT-Raman spectrum of a paracetamol based pain killer formulated as an effervescent powder compared to the "best" DRIFT spectrum

A further step in this process is demonstrated in Figure 7. Using the FT-Raman data, this shows a subtraction of the paracetamol tablet spectrum from that of the effervescent powder formulation. We are left with a sharp, clean spectrum of the remaining components, principally metoclopramide hydrochloride. It would be unthinkable to produce subtractions in this way from FT-IR data because the nature of the samples, in this case a solid tablet and a fine powder, have such a profound effect on the spectra produced. A change of phase in a FT-IR sample can be expected to cause bands to shift to higher and lower wavenumbers, to broaden and to change their relative intensities. Figure 7 illustrates the ease with which spectral subtractions can generally be used to simplify and separate multi-component systems using FT-Raman spectra. This also makes Raman spectra ideal for quantitative applications.

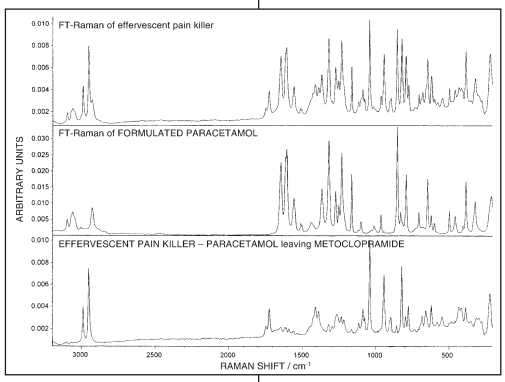

Figure 7: The subtraction of a paracetamol spectrum – measured from the tablet in solid form – from the effervescent powder. The residual shows metoclopramide and other ingredients

Figure 8 shows a comparison between FT-Raman and DRIFT FT-IR spectral measurements from a child's multivitamin capsule. The Raman spectrum, while still relatively "clean", is considerably more complicated than the other spectra shown so far. This may be explained by examining the contents of the capsule – the drug consists of a complex mixture of many ingredients suspended in a gel (Table 1).

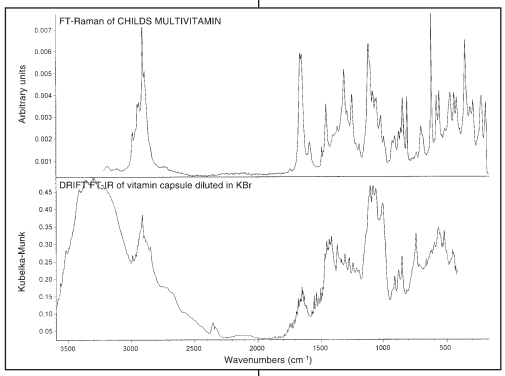

Figure 8: FT-Raman and "best" DRIFT spectra measured from a child's multivitamin capsule

Xylotal, Aspartame (sweeteners)
Ascorbic Acid (vitamin C)
Flavorings
Di-Calcium Phosphate
Gelatine
Vitamin A
Anti-oxidant (E307)
Cholecalciferole (Vitamin D3)

TABLE 1: Contents of the multivitamin tablet, Maltodextrin

It is extremely difficult to extract meaningful information from the FT-IR spectrum of the capsule contents. The band structure is again relatively complicated however, the gel and the dextrin included in the formulation exhibit strong, broad spectral features. In the FT-IR spectrum, these features mask much of the remainder of the spectral information; the FT-Raman spectrum however, is unaffected.

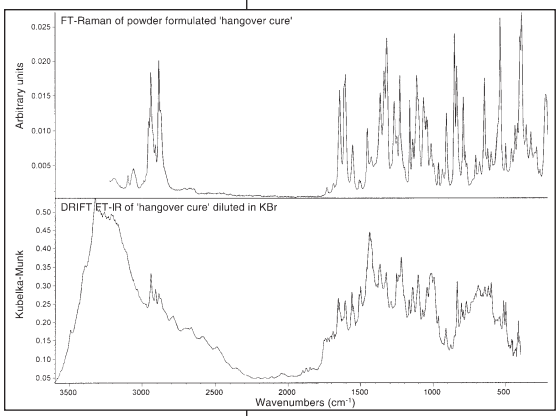

Figure 9: FT-Raman and "best" DRIFT spectra measured from a hang-over "cure" formulated as a powder

The final example shown in Figure 9 compares the FT-Raman and DRIFT FT-IR spectra recorded from an effervescent powder marketed as a "cure" for hangovers. The formulation not only contains a paracetamol painkiller, but also vitamins and components for causing the powder to react when added to water. The contents are listed in Table 2.

Paracetamol (1000 mg)
Anhydrous Citric Acid (1185 mg)
Sodium Bicarbonate (808 mg)
Potassium Bicarbonate (715 mg)
Sodium Carbonate (153 mg)
Vitamin C (30mg)
Glucose Base

TABLE 2: Contents of hang-over "cure"

Once again, we see a clean, clear FT-Raman spectrum and a DRIFT FT-IR spectrum dominated by broad bands. With the Raman data, the bands from the paracetamol are clearly distinguishable from others in the spectrum. The same is not true for IR. Although in this case, the Raman spectrum was measured from the gel inside the capsule. It is often possible to measure Raman spectra through the walls of pharmaceutical capsules. This works because the materials used for the capsule walls are often relatively weak Raman scatterers, and because the sample can easily be positioned so the spot most efficiently viewed by the instrument lies inside the capsule.

Conclusions

These experiments show that FT-Raman spectroscopy with NIR excitation lasers can have a variety of uses in the pharmaceutical laboratory. Raman is often ideal for the study of different isomer systems and for quantitative work. This note focused on the particular advantages FT-Raman offers in the study of formulated pharmaceuticals. For these materials

- Raman requires no sample preparation
- Raman is nondestructive
- The vibrational information derived from Raman spectra is different from that available in FT-IR
- Raman gives strong, clear spectra with short accumulation times
- Raman is unaffected by broad features which often mask useful spectral data in FT-IR measurements
- Raman allows subtractions to be made – even from samples of different forms

These are some of the reasons why Raman is becoming a widely used technique in the pharmaceutical industry.

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