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The application of Fourier-transform Raman spectroscopy to the analysis of pharmaceuticals and biomaterials*

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Abstract: Near infrared Fourier-transform (FT) Raman spectroscopy is shown to be a useful spectroscopic tool for the molecular structural analysis of drugs and biomedical polymers. The technique has been applied to the non-invasive investigation of the hydrolytic degradation of a biodegradable polymer in water over a period of 15 days and to the analysis of a drug within a polymer vehicle over a wide drug concentration range. This work demonstrates the potential value of FT Raman spectroscopy in the field of pharmaceutical science.

Keywords: *Near infrared Fourier-transform Raman spectroscopy; sympathomimetic amines; drug-polymers.*

Introduction

When a substance is irradiated with monochromatic light, the scattered energy consists almost entirely of radiation of the incident frequency (Rayleigh scattering). In addition, certain discrete frequencies above and below that of the incident beam are observed, a phenomenon known as Raman scattering (the measurement is relative to the Rayleigh frequency and is quoted in Raman shifts). Raman spectra are comparable with infrared spectra as both are concerned with measuring associated molecular vibrational and rotational energy changes. However, the requirement for vibrational activity in Raman spectra is a change in the polarizability of the molecule, in comparison to infrared spectra in which a change in the dipole moment is necessary. It is therefore possible to obtain spectral information of a homo-nuclear molecule by Raman spectroscopy [1].

The development of a near infrared Fourier-transform (FT) format for Raman spectroscopy has helped considerably to overcome the major problems previously experienced with this technique. Fluorescence, long spectral acquisition times and photodecomposition from extended exposure times have been successfully addressed and are now greatly reduced. The small sample requirement, minimal sample preparation and minimal sensitivity towards interference by water have made it possible to obtain Raman spectral data of white solids, opalescent solutions and aqueous media, and in conjunction with computer spectra subtraction, the matrix background can be removed to enhance a sample measurement [2].

In this short article, the potential of FT Raman for the analysis of three specific pharmaceutical systems is highlighted, viz. the analysis of drugs, in particular, sympathomimetic amines, the analysis of biomedical polymers, in particular, those known to undergo hydrolytic degradation, and the monitoring of drug concentrations within polymers, over a specified concentration range.

Materials and Methods

Instrumentation

The instrument used was a converted Perkin–Elmer series 1700 FTIR spectrometer

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with a 1064 nm Nd/YAG laser as the irradiating source [3]. The instrumental resolution for all the analyses was 6 cm^{-1}.

Drugs and chemicals

The sympathomimetic amines (arterenol, phenylephrine and ephedrine) were supplied by Sigma chemicals. The powdered drugs were placed in a cylindrical brass tube sample holder of 4 mm bore and minimum sample depth of 3 mm, and analysed at a laser power of 500 mW for 150 scans. The poly(anhydrides) were synthesized for the FT Raman studies in accordance with a method described elsewhere [4], and were analysed at 500 mW for 150 scans in the sample holder described above.

Degradation study

For the hydrolysis degradation study of poly(sebacic anhydride) the spectra were obtained from 3 × 3 mm rod samples stored in water for up to 15 days [5], and were analysed at 700 mW for 50 scans.

Drugs in polymers

A range of polymer matrices was prepared containing diclofenac (a non-steroidal anti-inflammatory drug) over a concentration range of 0.01–60% (w/w); these were analysed at 700 mW for 50 scans [5].

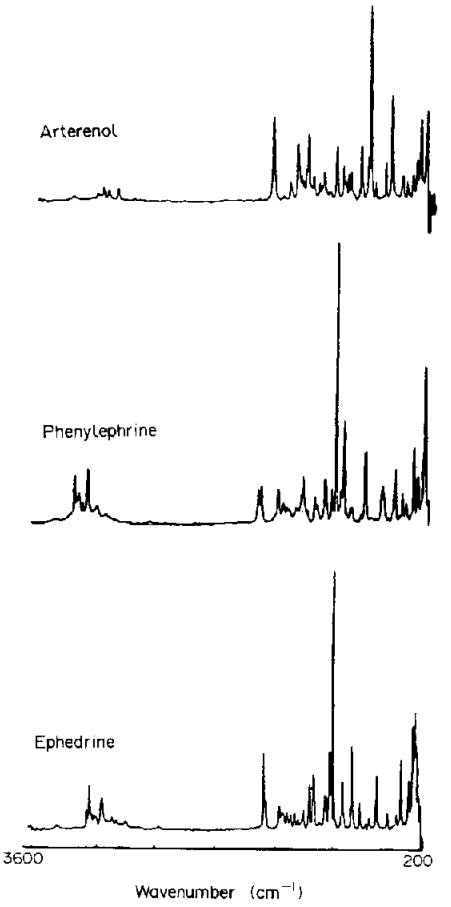

Figure 1
Comparison of the FT Raman spectra of three sympathomimetic amines over the range 3600–200 cm^{-1}.

Results and Discussion

Drugs

In this study, three drugs (ephedrine, phenylephrine and arterenol) were selected from a large series of chemically related sympathomimetic amines, to demonstrate the use of the technique for the characterization of drugs (Fig. 1). Each spectrum has a distinctive "fingerprint" region with good signal-to-noise ratio. Phenyl functional groups are good Raman scatterers and the frequency displacement pattern for each type of substitution is quite distinctive; for example the meta-disubstituted benzene group in phenylepherine can easily be identified by an intense polarized band near 1000 cm^{-1} due to the trigonal ring "breathing" vibration (996 cm^{-1}) together with weak Raman bands at 1260–1210 (1260 cm^{-1}), 1180–1160 (1166 cm^{-1}) and 1080–1060 (1080 cm^{-1}). In addition all phenyl groups show Raman bands at 3000–3100 cm^{-1} due to C—H stretching and also at 1500–1650 cm^{-1}. The bands associated with amine stretching are relatively weak and broad in all these spectra, and compared with the corresponding IR spectra are very weak. In contrast, the methylene stretching bands are easily discernible in all spectra. This study illustrates the use of FT Raman spectroscopy to differentiate between closely related compounds, and the use of this technique is currently under investigation for distinguishing different polymorphic forms of cimetidine.

Poly(anhydrides)

Langer *et al.* [6] have developed a series of poly(anhydrides) which biodegrade via an hydrolytic degradation of the polymer backbone to yield low molecular weight, non-toxic acids. By altering the carbon chain backbone of the polymer it is possible to change the degradation rate from periods lasting for months to that of years and hence control the release of a drug dispersed within. All anhydrides show two diagnostic carbonyl bands,

the band at the higher frequency is the more intense and is due to symmetric stretching of the carbonyl groups about the intermediate oxygen atom (i.e. CO—O—CO), and the band at the lower intensity is associated with the complementary asymmetric stretch. In general, the two bands are approximately 50–70 cm^{-1} apart regardless of where they are situated; for example poly(sebacic anhydride) (PSA; an aliphatic anhydride) has the carbonyl pairing at 1803/1739 cm^{-1} (sebacic acid shows only one carbonyl band in this region) whilst poly[bis(*p*-carboxyphenoxy) propane] (PCPP — an aromatic anhydride) has the pairing at 1764/1712 cm^{-1} (see Fig. 2). This demonstrates that it is possible to differentiate between the two types of anhydride bond, and further analysis of copolymer mixes of P(SA–CPP) at varying monomer levels appears to support this. In addition, the homo-polymers show distinctive methylene bands due to deformation, stretching, rocking and twisting, and the spectra for aromatic poly(anhydrides), such as PCPP, also show the diagnostic benzene para-substitution bands.

FT Raman may also be employed to study the degradation of these polymers in the solid state. The degradation study of poly(sebacic anhydride) in water over a 15-day period distinctly shows (Fig. 3) the anhydride band pair (1803/1739 cm^{-1}) diminish in intensity and

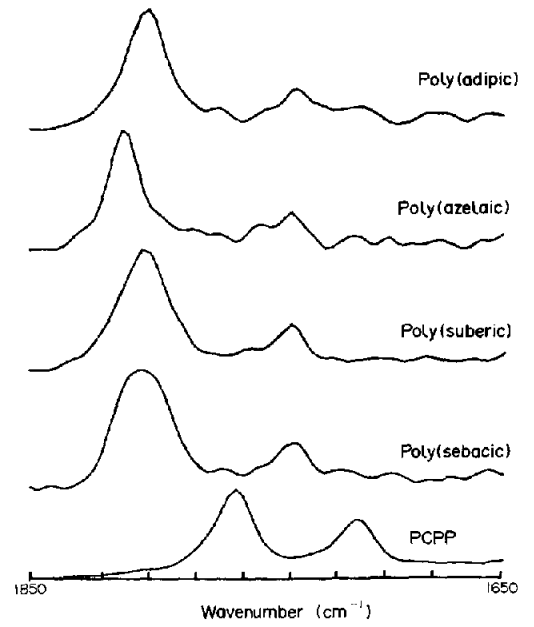

Figure 2
Comparison of the "anhydride" region for five poly (anhydrides).

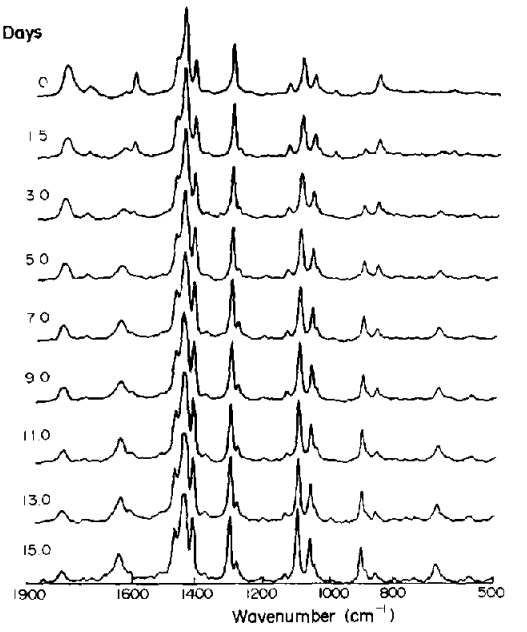

Figure 3
The FT Raman spectra of poly(sebacic anhydride) at various time intervals during the hydrolytic degradation study.

the emergence of a complementary acid carbonyl band (1640 cm^{-1}) which increases in intensity during the experimental period. This confirms that the degradation of these polymers occurs by reaction of the anhydride with water to give the corresponding acid. The spectra given here illustrate the potential for quantification of degradation kinetics in these polymers using FT Raman spectroscopy.

Drugs in polymers

Many different types of polymer-based drug-delivery systems are in current use, with the polymer acting as either a carrier or as the principal rate-controlling modulator of drug release. The physicochemical properties of both the polymer and the drug are both critical to the performance of these delivery systems and determine both the nature of the release process and the rate of diffusion of drug into the environment. With the previously mentioned advantages of FT Raman spectroscopy it is clear that such a technique can be employed to monitor changes in the physicochemical properties of such systems by non-invasive analysis. The FT Raman spectrum of diclofenac dispersed in a sodium alginate matrix shows strong bands due to the presence of the drug (Fig. 4); for example the two bands at 1578 and 1603 cm^{-1} are associated with the

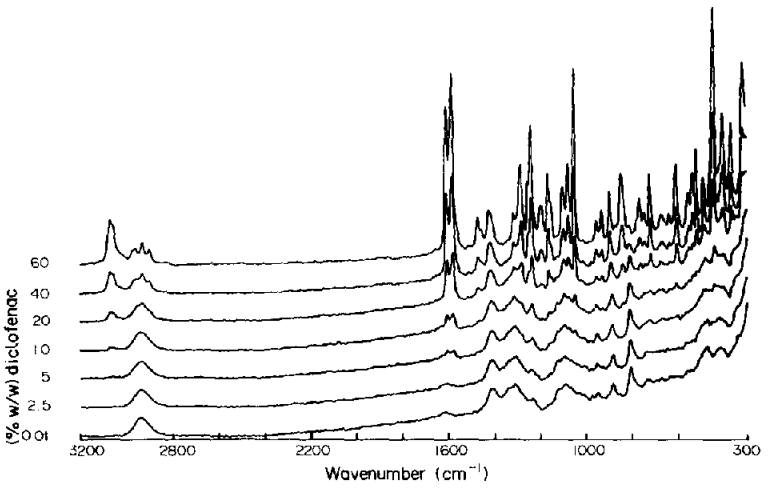

Figure 4
FT Raman spectra of diclofenac (0.001–60%, w/w) in sodium alginate.

aromatic groups within the structure of diclofenac. In contrast, the alginate has a relatively weak spectrum, a consequence of the poorly-scattering groups within the molecule. As expected, changes in the concentration of diclofenac result in corresponding changes in the intensities of the drug-associated peaks such as the aromatic bands at 1578 and 1603 cm^{-1} mentioned previously, the peak intensity at these wavelengths being related to the concentration of drug present. Further details of this study are given elsewhere [5], but the major feature is the apparent ability to detect both qualitatively and quantitatively the Raman bands characteristic of the molecular structure of a drug and the study serves to show the value of FT Raman spectroscopy for the *in situ* solid state analysis of drug delivery systems.

General Overview and Future Considerations

Although this article is brief, it highlights the potential of FT Raman spectroscopy in the area of pharmaceutical science. It is particularly useful as an analytical tool for drug molecules that contain groups that are strong Raman scatterers, for example phenyl and other aromatic moieties (which the majority of drug molecules possess). It is a complementary technique to established instrumental methods, such as mass spectrometry and NMR, but analysis does not always result in sample destruction. The recent introduction of FT Raman microscopy and fibre optics for remote sensing holds considerable promise [7, 8].

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