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FT Raman spectroscopy of drugs in polymers

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Summary

The value of Fourier transform Raman spectroscopy in quantifying drug/polymer mixtures is demonstrated. Spectra of promethazine, diclofenac, theophylline and indomethacin in polymeric diluents based on polyethylene oxide, sodium alginate and hydroxypropylmethylcellulose are given.

Introduction

Polymers are widely employed as biomaterials and are heavily utilised in the design of drug delivery systems. There are many different types of polymer-based drug delivery systems in present use, but in general the polymer functions either as a carrier or as the principal rate-controlling modulator of drug release, enabling the device to provide prolonged release over periods of time ranging from hours to several months. The physicochemical properties of both polymer and drug are critical to the in-life performance of these dosage forms, determining, for example, the nature of the release process or the rate of diffusion of drug through the polymer and into the surrounding environment. The development of techniques for the in-situ solid state analysis of the components within polymeric drug delivery devices is therefore an important goal, both for the characterization of these systems, and for the study of the influence of physicochemical properties on the mode and kinetics of drug release. For example, a technique which is capable of providing a quantitative analysis of drugs or polymers within the dosage form, may subsequently provide a means for monitoring the diffusion and dissolution of drug from the device, and also perhaps the accompanying changes in the polymeric environment. This would provide a powerful tool with which to investigate the fundamental mechanisms controlling drug release from a particular dosage system.

Several techniques have been recently utilised to characterise drug delivery systems in the solid state. These include solid state NMR (Azoury, 1988), Fourier transform (FT) infrared (IR) spectroscopy (Nylias and Ward, 1977) and differential

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scanning calorimetry (Castelli et al., 1989).

Raman spectroscopy also exists as a potentially powerful method for the molecular analysis of polymers (Gerrard, 1984) and biological molecules (Carey, 1983). In this technique, the specimen is illuminated with monochromatic radiation of frequency ν_0 and the resultant scatter is analysed for inelastic components. These are very weak and are red-shifted with frequencies $\nu_0 - \nu_{vib}$ where ν_{vib} are the Raman-active molecular vibrational frequencies. Blue-shifted Raman scatter also occurs, but is weaker. A good review of the technique will be found in Colthup et al. (1975). Raman spectroscopy supplies distinct molecular and structural information, and the acquisition of data is rapid. The technique is usually non-destructive, there are no special requirements for sample preparation and it allows optically imperfect samples to be analysed; an important criterion for solid state samples (Carey, 1982). The widespread application of Raman techniques has been hindered by two major problems; fluorescence and colour. When illuminated with a laser, many complex organic compounds fluoresce and should this occur, the intensity of the fluorescence is normally much greater than that of the Raman scatter, and the latter is obscured. Furthermore, many non-fluorescent materials also exhibit a low-level inelastic broad-band emission which is sufficiently intense to obscure the Raman spectrum (Spiro, 1987). It is this latter effect that has hampered the study of polymer degradation and especially the study of many biologically-significant materials or organic molecules in biological environments. In addition, if a compound or its environment are coloured, absorption of the laser source can occur and this frequently makes Raman spectroscopy impossible. The overall consequence is that to date, Raman spectroscopy has not contributed significantly to our fund of knowledge.

It has recently been shown (Cutler, 1990; Davies, 1990) that the problem of fluorescence may be largely overcome by employing a near-infrared laser as the excitation source with the subsequent Raman scatter being processed by the use of an interferometer (Hendra and Mould, 1988). Electronic transitions from the ground state are rare in the infrared spectral domain and as such preclude the fluorescence phenomenon in the majority of cases. In addition, the lower energy photons of this spectral region are less likely to incite significant amounts of photochemical degradation.

FT Raman spectroscopy may therefore possess a previously untapped potential for the analysis of drugs distributed within a polymer network. In this paper we report on the use of FT Raman spectroscopy for the detection and analysis of some common pharmaceutical polymers and drugs distributed within a polymer matrix. The results represent both a quantitative and qualitative assessment of some drug compounds incorporated into a compressed polymer matrix. This is one of the simplest, but effective and widely-used, design of controlled release drug delivery system.

Materials and Methods

Materials

Sodium diclofenac ([2-(2,6-dichloroanilino)-phenyl]acetic acid), indomethacin (1-(4-chlorobenzoyl)-5-methoxy-2-methylindol-3-yl-acetic acid), promethazine hydrochloride (10-(2-dimethylaminopropyl)phenothiazine) and theophylline (1,3-dimethylxanthine) were obtained from Sigma, U.K. The molecular structures of these compounds are shown in Fig. 1. Sodium alginate (manugel DPB) was supplied by Kelco International Ltd, U.K., hydroxypropylmethylcellulose (HPMC K4M) by Dow Chemical Co., Basle, Switzerland, and polyethylene glycol by BDH Chemicals, Poole, U.K.

Methods

All materials used in these studies were of particle size 125–180 μm. The drug:polymer matrices were prepared as follows. A series of homogenous dry powder mixtures (batch size 5 g) were prepared according to the formulae in Table 1, by hand-blending and then mixing in a vibratory mixer for 10 min. The blends were compressed into flat-faced 3 mm diameter tablets using a Manesty F3 single punch tablet machine.

Raman spectra were acquired using a Perkin Elmer 1710 FT-IR spectrometer optimised for the near-infrared spectral region, as described pre-

TABLE 1

Formulations prepared for analysis (% w/w concentrations)

Sample no.	Diclofenac (sodium)	Theophylline	Promethazine (hydrochloride)	Indomethacin	Sodium alginate	HPMC	PEG
1	–	20.00	–	–	80.00	–	–
2	–	–	20.00	–	80.00	–	–
3	–	–	–	20.00	80.00	–	–
4	20.00	–	–	–	–	80.00	–
5	20.00	–	–	–	–	–	80.00
6	00.01	–	–	–	99.99	–	–
7	00.50	–	–	–	99.50	–	–
8	1.00	–	–	–	99.00	–	–
9	2.50	–	–	–	97.50	–	–
10	5.00	–	–	–	95.00	–	–
11	20.00	–	–	–	80.00	–	–
12	40.00	–	–	–	60.00	–	–
13	60.00	–	–	–	40.00	–	–

viously (Crookell et al., 1990). In summary, the laser excitation source is a continuous wave Nd-YAG laser with an output at 1.064 μm. The power of the laser on the sample was in the range 200 mW and all spectra were recorded at 6 cm^{-1} resolution using 50–100 accumulated scans. The samples were retained as solids in a small cup 3 mm in diameter and approx. 2 mm deep, and the time required to load the sample and record the spectrum was only a few minutes, usually less than 5 min.

Infrared spectra were acquired by diffuse reflectance using a Nicolet 740 FT-IR spectrometer with a germanium-coated potassium bromide beam splitter. Each spectrum represents 257 scans with a scan time of 86 s.

Results and Discussion

FT Raman spectroscopy of drugs

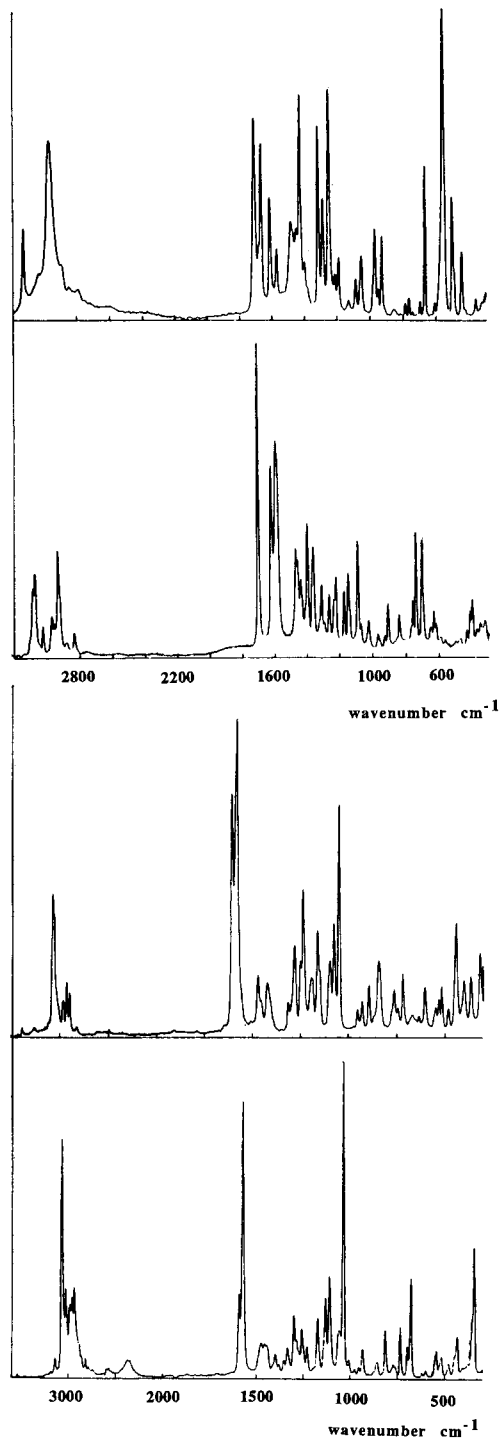
The Raman spectra of the drugs are presented in Fig. 1 and compared with their infrared adsorption spectra equivalents in Fig. 2. The spectra obtained illustrate several important aspects of Raman, in particular in relation to infrared spectroscopy:

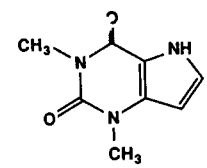
(a) In the same way as infrared spectra, the Raman spectra are 'fingerprints' and thereby may be potentially useful for detecting the presence of the drugs and their molecular structures within other environments.

(b) Molecular vibrations normally give rise to both infra-red and Raman bands but their intensities are very different, and the prominent 'group frequencies' familiar to infrared users, do not appear reliably in the Raman spectrum and vice versa. As a consequence it should be emphasised that both infrared and the Raman spectra should be acquired if molecular vibrational analysis is to be used to the full. Whilst this point is well understood and has been noted before (Terpinski et al., 1987), its relevence has been restricted by the difficulty of obtaining Raman spectra. However, the relative ease with which FT Raman spectra can be recorded perhaps makes the point worthy of restatement.

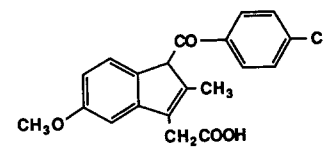
(c) Individual features of the Raman spectra may be used to indicate the presence of specific chemical groups, as with infrared. This is illustrated below.

(d) In general, whilst the intensity of the infrared absorption of all compounds varies little (a film between 25 and 100 μm thickness of any pure compound will give a reasonable spectrum) in Raman spectroscopy this is not the case. Some compounds are extremely good scatterers, others are weak, and the intensity ratio between the two extremes may span more than two orders of magnitude. Examples are readily found in the literature (Bourgeois and Church, 1990; Hodges and Akhavan, 1990) but as will be shown, this intensity difference can be exploited in the analysis of drug

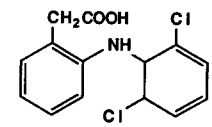




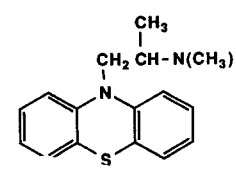
THEOPHYLLINE



INDOMETHACIN



DICLOFENAC



PROMETHAZINE

Fig. 1. FT Raman spectra of four common drugs.

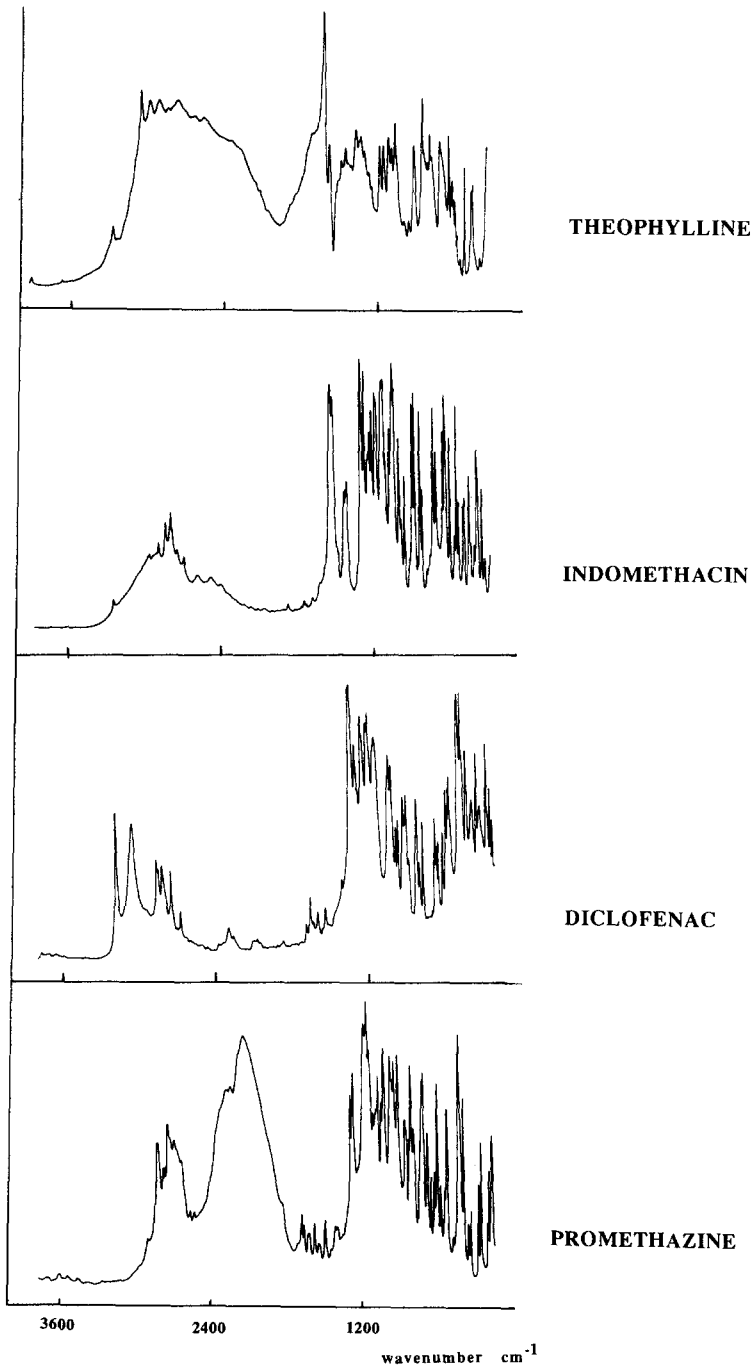


Fig. 2. Infrared spectra of four common drugs.

delivery systems.

With the exception of theophylline, the drug structures contain a benzene ring and the Raman spectra of these drugs thereby exhibit intense bands at frequencies between 1560–1620 cm^{-1} characteristic of aromatic ring stretching (Robin-

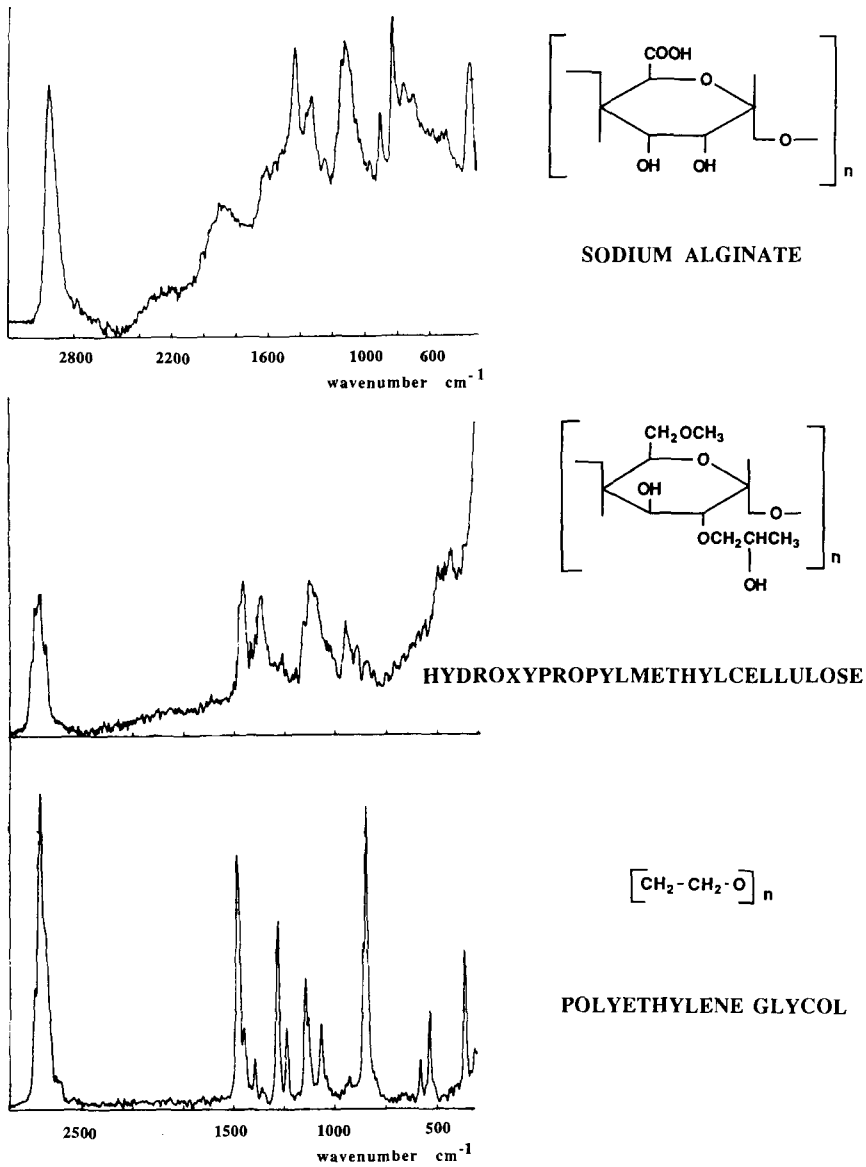


Fig. 3. FT Raman spectra of polymers used to support the drugs shown in Fig. 1.

son, 1984). No such bands appear in the spectrum of theophylline. In addition, the Raman spectra exhibit bands in the region 3100–3000 cm^{-1} characteristic of both aromatic C-H and aliphatic $=CH_2$ stretching modes, and also bands in the region 2969–2850 cm^{-1} which are attributable to aliphatic CH_3, CH_2 stretching.

FT Raman spectra of polymers

FT Raman spectroscopy of the individual polymer components of the matrices, sodium alginate, hydroxypropylmethylcellulose (HPMC) and polyethylene glycol (PEG), gave rise to the spectra shown in Fig. 3.

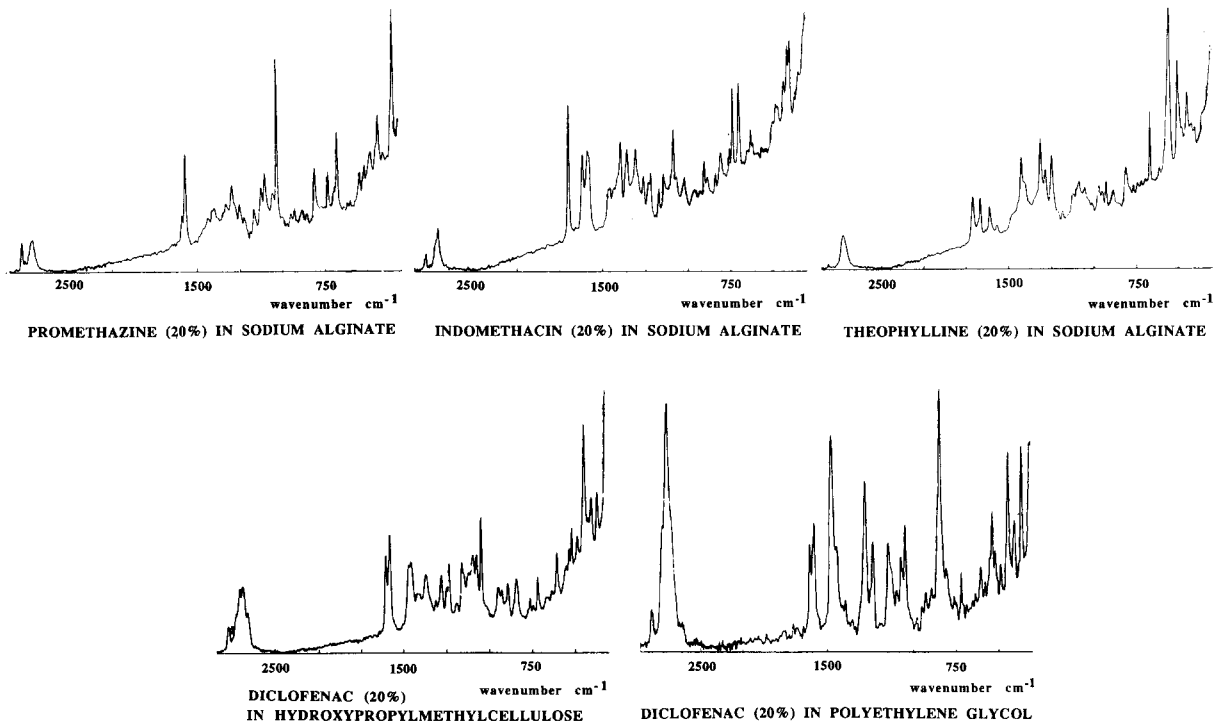


Fig. 4. FT Raman spectra of drug/polymer matrices.

The Raman spectrum of PEG is well known and the spectrum in Fig. 3 is typical. The well defined spectrum shown is specific for the crystalline material (Joyce et al., 1977) and any reduction in the structural order, for example by dissolving the PEG in water, leads to a broadening of the spectrum (Hartley et al., 1977).

In general, ionic materials and heavily hydroxylated species, particularly if of poor morphology tend to show weak broad spectra, arising from the multiplicity of overlapped Raman bands. The spectra of sodium alginate and HPMC are typical of such materials.

FT Raman spectra of drug-containing polymer matrices

Typical Raman spectra acquired from the drug: polymer matrices are shown in Figs 4 and 5. It is evident that many of the prominent spectral features observed for the pure drugs can also be seen in the drug:polymer spectra. All four drugs were detectable in sodium alginate at the level of 20% w/w and the prominent features of the Raman spectrum of sodium diclofenac were clearly visible in the three different polymers. In particular, compounds containing aromatic structures such as these drugs, are more efficient Raman scatterers than the polymers where these types of structures are absent, and the aromatic bands provide a particularly valuable distinguishing feature which facilitates the detection of drugs in the mixture. The presence of characteristic bands specifically attributable to the drug and polymer components illustrates the usefulness of FT Raman spectroscopy for the in-situ solid state analysis of drugs and polymers in these systems.

A subtraction of the polymer component from the drug:polymer spectrum, is shown in Fig. 5 for the sodium diclofenac:sodium alginate combination. A comparison of this subtracted spectra with that for the pure drug (Fig. 1) shows that there appears to be no shifts in the prominent Raman peaks of the drug. However, if the spectrum of the pure sodium diclofenac is subtracted

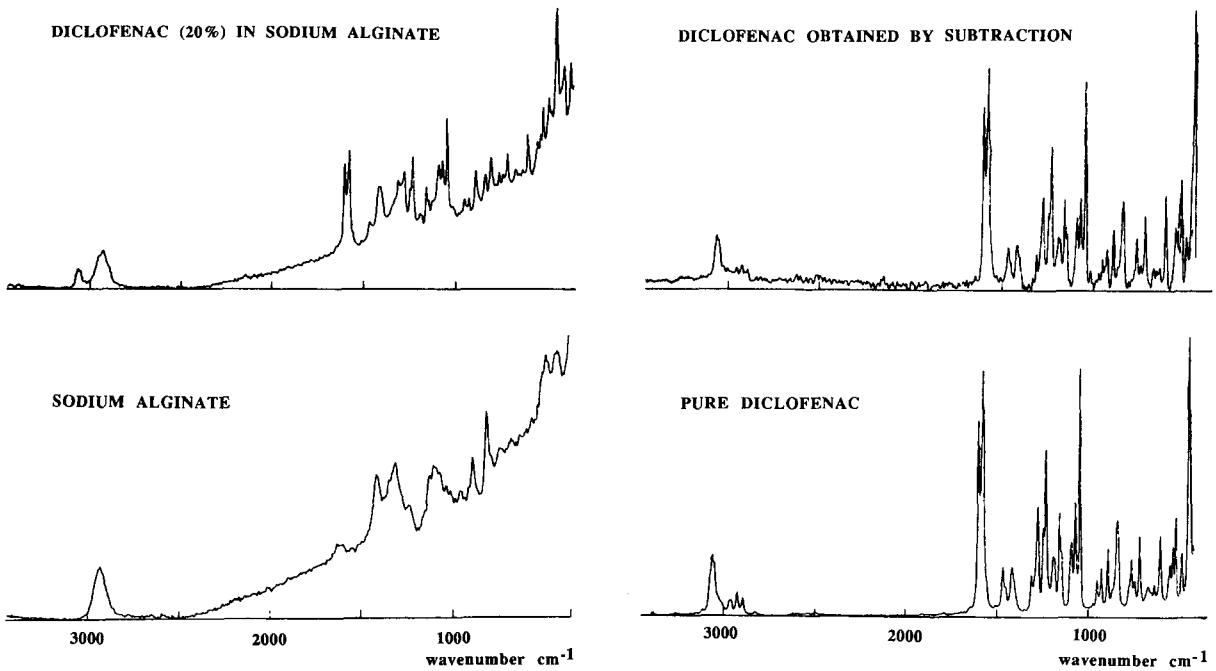


Fig. 5. Comparison of the Raman spectrum of pure diclofenac with that obtained by subtraction.

from that of the combination in order to retrieve the spectrum of alginate, small shifts are observed in the alginate spectrum (in the order of 1 cm^{-1}) are observed. It is suggested that these may be due to physical interactions between the drug and polymer, possibly Van der Waals forces.

FT Raman spectroscopy of diclofenac/alginate matrices — a quantitative analysis

A series of matrices containing diclofenac 0.01–60.0% (w/w) in sodium alginate were analysed. The spectra are shown in Fig. 6 and the intensity of those peaks in the Raman spectra corresponding to the drug molecule appear to show a concentration-dependent change.

In order to quantify these changes, two bands specific for the drug at 1578 and 1603 cm^{-1}, were integrated at each drug concentration. The relationship between the band integrated intensity and the concentration of diclofenac in the polymer matrix is shown in Fig. 7 and there is a clear linear relationship between the two over the concentration range 5–60% drug ($r = 0.999$). However, this line does not extrapolate to the origin suggesting that a degree of drug:substrate interaction may be occurring. The lower limit of detection of drug appeared to be within the region of 0.5% w/w and below a 5% w/w drug concentration, the plot exhibits a degree of curvature. Measurements at these concentrations are relatively imprecise because of the very low signal/noise ratio.

Conclusions

FT Raman spectroscopy applied to the analysis of individual drugs and polymers reveal spectra which are qualitative fingerprints diagnostic of the molecular structures of the materials. Similarly, an analysis of drug:polymer mixtures resulted in composite spectra equivalent to an overlay of the spectra of the individual components. A quantitative analysis of drug within a polymer matrix has been achieved by FT-Raman for the first time over a wide range of concentrations and the results confirm a clear relationship between the concentra-

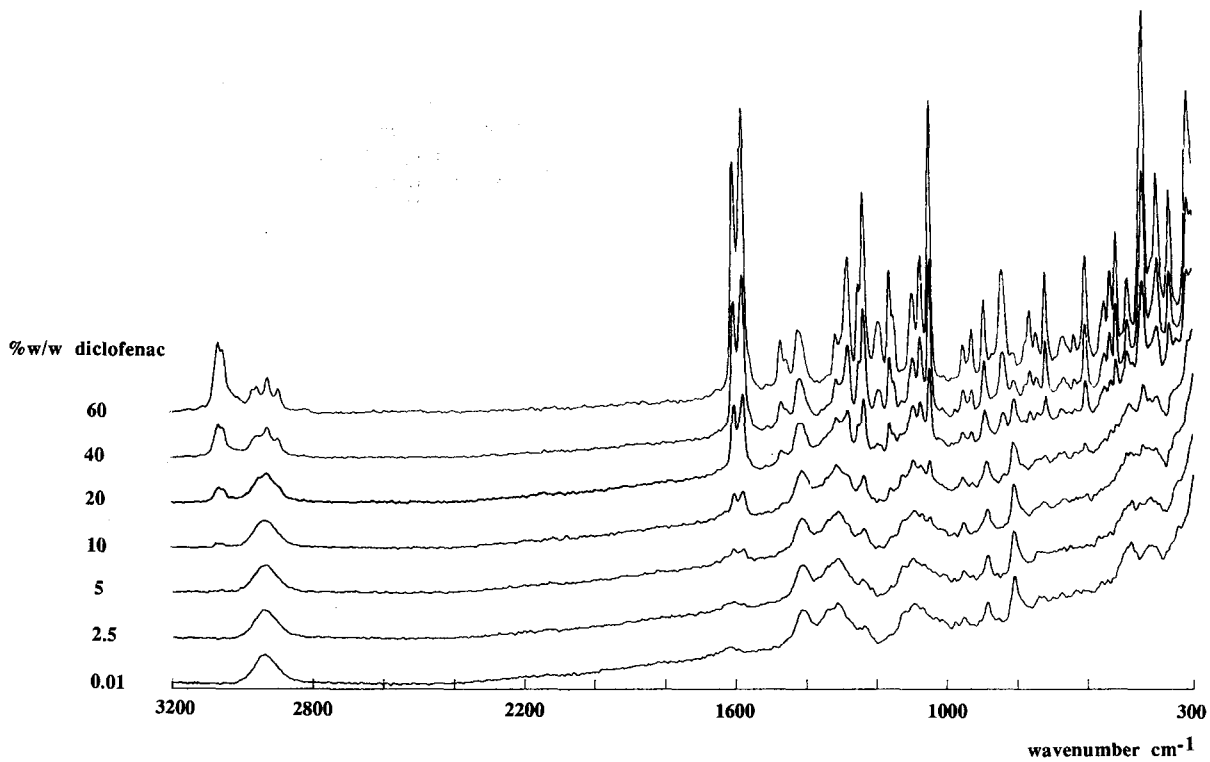


Fig. 6. FT Raman spectra of diclofenac (0.01–60% w/w) in sodium alginate.

tion of drug and the intensity of prominent bands in the Raman spectrum attributable to the drug. This work illustrates the potential of Raman spectroscopy for the in-situ solid state characterization of drugs within polymers. In particular, the results demonstrate the ability of the technique to distinguish and quantify the levels of bioactive components in polymeric drug delivery systems, provided that strong distinguishing features between the spectra of the components exist. The specific value of this new near infrared excited FT Raman method lies in its convenience and the lack of interference from fluorescence in commercial samples. The technique is considered to be complementary and in some cases, superior to infrared spectroscopy because of the ease of sample preparation and the lack of interference from water which may be present in certain samples (Gerrard, 1984). The additional facility of comparing the drug spectra both in the pure form and that within the polymer matrix (after subtraction) allows for the detection of any shifts in the peak positions and intensities which are indicative of a change in the chemical environment of the drug molecules. This may occur through a polymer-drug interaction and hence, FT-Raman may make

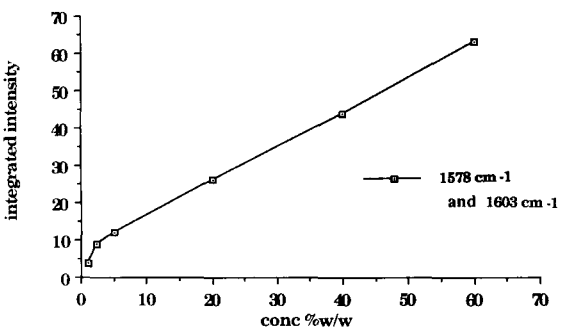


Fig. 7. Relationship between band intensity (integrated) at 1578 and 1603 cm^{-1} and concentration of diclofenac (drug) in sodium alginate (matrix).

a significant contribution in the analysis of the solid state interactions of strongly scattering pharmaceuticals.

This study strongly suggests that FT Raman spectroscopy may have considerable potential for the quantitative analysis of changes in drug concentration over the duration of the drug release from these systems. This would allow drug diffusion and dissolution to be monitored within the device in situ and hence provide evidence for the fundamental mechanisms controlling the release of drug. Until very recently, access to FT-Raman instrumentation has been limited to a few specialised laboratories with home grown or adapted equipment. The recent advent of commercially-available FT-IR/Raman systems should broaden the techniques application within the Pharmaceutical and Biomedical Sciences.

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References

Azoury, R., Elkayam, R. and Friedman, M., Nuclear magnetic resonance study of an ethylcellulose sustained release system. I: Effect of casting solvent on hydration properties. *J. Pharm. Sci.*, 77 (1988) 425–431.

Bourgeois, D. and Church, P., Studies of dyestuffs in fibres by fourier transform raman spectroscopy. *Spectrochim. Acta,* 46A (1990), 295–301.

Carey, P., *Molecular Biology: Biochemical Applications of Raman and Resonance Raman Spectroscopy*, Academic Press, New York, 1982.

Carey, P., Raman spectroscopy for the analysis of biomolecules. *Trends Anal. Chem.*, 2, (1983) 275–277.

Castelli, F., Puglisi, G., Pignatello, R. and Gurriieri, S., Calorimetric studies of the interaction of 4-biphenylacetic acid and its cyclodextrin inclusion compound with lipid model membrane. *Int. J. Pharm.*, 52 (1989) 115–121.

Colthup, N.B., Daly, L.H. and Wiberley, S.E., *Introduction to Infra Red and Raman Spectroscopy*, 2nd Edn, Academic Press, London, 1975.

Crookell, A., Hendra, P.J., Mould, H.A. and Turner, A., Fourier transform raman spectroscopy in the near infra-red region. *J. Raman Spectrosc.*, 21, (1990) 85–91.

Cutler, D.J., Fourier transform raman instrumentation. *Spectrochim. Acta*, 46A (1990) 131–151.

Davies, M.C., Binns, J.S., Melia, C.D. and Bourgeois, D., Fourier transform Raman spectroscopy of polymeric biomaterials and drug delivery systems. *Spectrochim. Acta*, 46A (1990) 277–283.

Gerrard, D.L., Raman spectroscopy and polymer analysis, *Chemistry in Britain*, 1984, pp. 719–715.

Hartley, A.J., Leung, Y.K., Booth, C. and Shepperd, I.W., Raman scattering from mixtures of poly(ethylene oxide) 2000 with poly(ethylene oxide) 200. *Polymer*, 18 (1977) 336–340.

Hendra, P.J. and Mould, H.A., Fourier transform Raman spectroscopy as a routine analytical tool. *Int. Lab.*, Sept. (1988) 34–45.

Hodges, C.M. and Akhavan, J., The use of Fourier transform Raman spectroscopy in the forensic identification of illicit drugs and explosives. *Spectrochim. Acta*, 46A (1990) 303–307.

Joyce, E., Mulley, R.D., Pafe, G.A., Booth, C. and Shepperd, I.W., Raman scattering from the longitudinal acoustic modes of crystalline poly(ethylene oxide) swollen by oligomers of various molecular weights. *Polymer,* 18 (1977) 1190–1191.

Nylias, E. and Ward, R.S., Development of blood compatible elastomers. V. Surface structure and blood compatibility of avcothane elastomers. *J. Biomed. Mat. Res. Symp.*, 8 (1977) 69–84.

Robinson, J.W., *Handbook of Spectroscopy*, Vol. II, CRC Press, 1984.

Spiro, T.G., *Biological Applications of Raman Spectroscopy*, Vols I and II, Wiley, New York, 1987.

Terpinski, J., Baranska, H. and Labadjinska, A., *Laser Raman Spectroscopy*, Ellis Harwood, Chichester, 1987.