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Short Communication

Quantitative determination of $CaCO_3$ and glycine in antacid tablets by Laser Raman Spectroscopy

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Introduction

There is an ever growing need for fast and reliable quantitative methods to determine the ingredients of a commercial drug. Laser Raman Spectroscopy (LRS) has been proved to be an excellent non-destructive tool, not only for qualitative purposes, but also for quantitative analysis. Applications of this spectroscopic method include a variety of topics, such as studies on the polymorphism of cortisone acetate [1], the quantification of drugs in drug–polymer mixtures [2], the quantitative determination of different crystal phases of a compound [3] and the quantitative determination of acetyl salicylic acid as a single active ingredient in tablets [4].

In the present work, LRS was used for the simultaneous quantitative and non-destructive determination of two active ingredients, calcium carbonate and glycine, in a commercially available antacid tablet, based on a single spectrum. Calcium carbonate is a fast action antacid, while glycine, which is an ampholyte, acts as a buffer in order to prolong the effect of $CaCO_3$. The usual assay for calcium carbonate [5] involves heating to constant weight, addition of HCl, dilution with water and addition of NaOH. Finally titration is carried out with disodium ethylenediaminetetraacetate using hydroxy naphthol blue as indicator. The assay for glycine requires addition of glacial acetic acid and titration with perchloric acid using crystal violet as indicator [6]. Both assays are time consuming, which is a major drawback, especially for the routine analysis of tablets in a production line, where the demand for high precision is not required.

In the present work, the quantities of calcium carbonate and glycine in tablets were successfully determined by using the ratio of the intensities of two easily defined LRS peaks for these two ingredients. For this purpose, a calibration curve was obtained, by mixing known quantities of the two species, and a linear relationship is proposed for calculating the amount of each component.

Materials and Methods

Sample preparation

Commercial tablets of Riker Laboratories (Loughborough, UK) under the name Titralac® containing only two ingredients, 180 mg glycine and 420 mg calcium carbonate, were purchased locally. The spectrum of commercial tablets spectrum (Fig. 1c) indicates that the crystal phase of the $CaCO_3$ used by the manufacturer was calcite (C.G. Kontoyannis, unpublished results on $CaCO_3$ phases with LRS), which is thermodynamically the most stable phase of calcium carbonate. Thus, the same crystal phase was used in the experiments and was prepared according to [7]. Glycine was obtained from 'Fluka AG' (Buchs, Switzerland). In order to construct a calibration curve, mixtures of glycine and calcium carbonate were prepared in the correct stoichiometric ratios, using an agate mortar (Table 1). The pure powders were dried at 120°C for 24 h

Table 1
Relative intensity ratios of the 1088 to 893 cm^{-1} peaks for $CaCO_3$-glycine tablets

Molar fraction of $CaCO_3$ in $CaCO_3$-glycine tablets	I^{1088}/I^{893}*	Relative standard deviation (%)
0.05	0.14	4.90
0.15	0.42	4.48
0.25	0.75	3.61
0.35	1.22	2.76
0.45	1.92	2.98
0.55	2.88	3.43
0.65	4.11	4.08
0.75	6.89	4.36
0.85	13.00	4.86
0.95	43.51	5.03
Commercial tablet 1 (0.64)†	4.12	3.10
Commercial tablet 2 (0.64)†	4.25	3.26
Commercial tablet 3 (0.64)†	4.16	2.92

*The intensity ratio is the average of values obtained from four spectra, for the $CaCO_3$ line and the glycine line, respectively.
†According to manufacturer's specifications for each tablet.

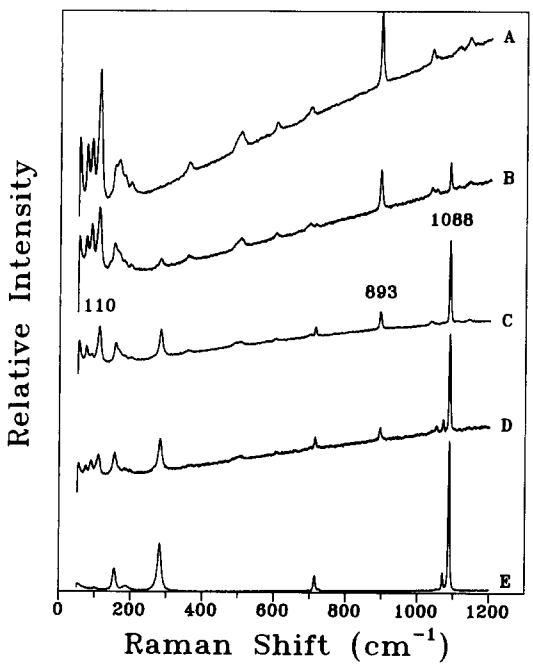

Figure 1
Raman spectra of tablets from (A) Glycine; (B) mixture of 25 mol% $CaCO_3$ with 75% glycine; (C) commercial tablet with 180 mg glycine and 420 mg $CaCO_3$; (D) mixture of 75 mol% $CaCO_3$ with 25% glycine; (E) $CaCO_3$ (calcite phase). Spectra were excited at 20°C with an argon laser; λ_0 = 488.0 nm; spectral slit-width, 1 cm^{-1}.

prior to use. The mixtures were pressed to tablets using a standard pellet press. The homogeneity of the pellets was verified by obtaining several spectra for each pellet, from different points on the surface. Commercial tablets were used with no further treatment.

LRS (system configuration)

Raman spectra were excited with the 488-nm line of a 4 W Spectra–Physics argon laser. The plasma lines were removed from the laser beam by using a small monochromator as filter. A cylindrical lens, with 127 mm focal length, was used to focus the laser line on the sample, giving a probed area of approximately 1 mm^2. The scattered light was collected at an angle of 90° and analysed with a SPEX 1403, 0.85 m double monochromator equipped with a RCA photomultiplier cooled to −20°C; a EG&G/ORTEC electronic amplifier using photon-counting was used. The power of the incident laser beam was about 100 mW distributed over the surface of the sample. Typical spectral width and time constant values were 1 cm^{-1} and 3 s, respectively. The system was interfaced, through an DAS-16 data acquisition card (Omega, USA), with a computer, and spectra were recorded by X-T recorder's and simultaneously digitized and stored in diskettes.

Results and Discussion

Construction of the calibration curve

The objective was to find an easy and a reliable method to calculate the percentage of each ingredient. For this purpose, the peak height was used and not the integrated intensities of the bands. The marked differences in the measured intensities of the bands in the various spectra (Fig. 1) made it apparent that only *relative factors* within each spectrum, e.g. ratio of the intensities, could be used.

The spectrum of the $CaCO_3$ powder as calcite (Fig. 1E) exhibits the strong C-O stretch band at 1088 cm^{-1} while the most characteristic bands of pure glycine are those at 110 and 893 cm^{-1} (Fig. 1A). Although the 110 cm^{-1} peak appears to be stronger than that at 893 cm^{-1}, the latter was chosen for the quantitative determination since its background was easier to define.

The intensity of a Raman line depends on a number of factors, including incident laser power, frequency of the scattered radiation, absorptivity of the materials involved in the scattering and the response of the detection system. Thus, the measured Raman intensity, I^{ν}, can be represented [8] as

$$I^{\nu} = I_0 K^{\nu} C \qquad (1)$$

where I_0 is the intensity of the excitation laser line, ν is the Raman frequency shift (cm^{-1}), K^{ν} is factor which includes the frequency dependent terms: the overall spectrophotometer response, the self-absorption of the medium and the molecular scattering properties. C is the concentration of the Raman active species as mole fraction.

If $\chi_{glycine}$ and χ_{CaCO_3} are the molar fractions of glycine and calcium carbonate, respectively, then for the glycine-$CaCO_3$ pellets their relationship should be: $\chi_{glycine} + \chi_{CaCO_3} = 1$. Thus, the ratio of the relative intensity of the 1088 cm^{-1} calcium carbonate peak to the relative intensity of the 893 cm^{-1} glycine peak can be represented as

$$\frac{I^{1088}}{I^{893}} = \frac{K^{1088}}{K^{893}} \frac{1}{\chi_{glycine}} - \frac{K^{1088}}{K^{893}}, \qquad (2)$$

where I^{1088} (for $CaCO_3$) and I^{893} (for glycine) represent the intensities of the 1088 and the 893 cm^{-1} peaks, respectively. The superscript on K represents the Raman frequency shift of the peak.

The plot of the ratio of I^{1088}/I^{893} vs the $\chi^{-1}_{glycine}$ is shown in Fig. 2. The exact molar fractions and the intensity ratio of the compositions plotted in Fig. 2 are as shown in Table 1. It should be noted that the intensity ratio used in Fig. 2 represents the average intensity of four Raman spectra. The relative standard deviation (RSD) values, expressed as a percentage, for averaged intensity ratios were also calculated (Table 1).

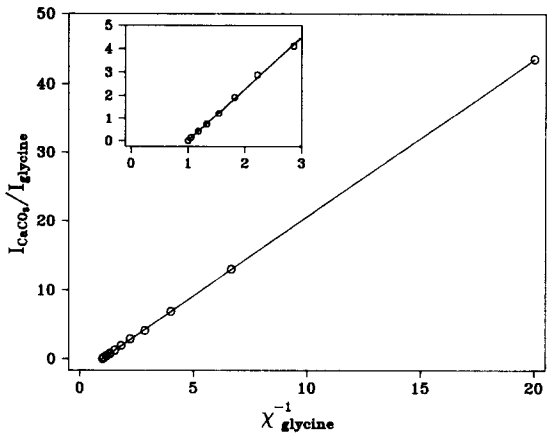

Figure 2
Plot of the I^{1088}/I^{893} ratios vs $\chi^{-1}_{glycine}$, where $\chi_{glycine}$ is the molar fraction of the glycine.

The values of both intensities were obtained after subtracting the "background" intensity. Typical spectra of pellets with different percentages of $CaCO_3$ and Glycine are shown in Fig. 1.

As indicated in Fig. 2, the data are linear and regression analysis yields the following equation

$$\frac{I^{1088}}{I^{893}} = \frac{1}{\chi_{glycine}} 2.29 - 2.29. \qquad (3)$$

The correlation coefficient was 0.999 while the standard errors for the slope and the intercept were $\pm 6.2 \times 10^{-4}$ and $\pm 1.6 \times 10^{-3}$, respectively.

In the range of our spectra measurements, the overall spectrometer response can be considered to be constant, and thus the K ratio is dependent only on the scattering parameter associated with each band, provided that it can be assumed that significant absorption of the exciting radiation does not occur. Consequently, the value assigned to the K ratio can be used regardless of the Raman spectrometric system used, provided that the 488-nm excitation line of an Ar laser is used.

Determination of glycine and $CaCO_3$ in commercial tablets

The average I^{1088}/I^{893} ratios for three Titralac® tablets are shown in Table 1. The values were calculated from four spectra obtained for each tablet. No significant difference was observed for the glycine content in each of the three samples. The molar fraction of glycine was calculated from equation (3) using the

I^{1088}/I^{893} ratios of the antacid tablets and found to be equal to 0.36 for each of the tablets 1 and 2, and 0.35 for tablet 3. The expected value, according to the manufacturer, was 0.36. From the RSD values in Table 1, the standard errors were calculated for the slope and intercept of equation (3), and using the error propagation theory [9] the RSD, expressed as a percentage, for the $\chi_{glycine}$ content in commercial tablets 1, 2 and 3 was found to be 2.3, 2.5 and 2.1, respectively. The molar content of calcium carbonate was found by difference to be 0.64 (tablets 1 and 2) and 0.65 (tablet 3), respectively.

Conclusions

A method for the simultaneous measurement of the percentage of glycine and calcium carbonate in antacid tablets, has been developed using Raman spectroscopy with an argon laser. The plot of the intensity ratio of the 1088 cm^{-1} peak ($CaCO_3$) to the 893 cm^{-1} peak (glycine) against the reciprocal of the molar fraction of glycine was found to yield a straight line. The potential of LRS is clearly demonstrated as a non-destructive quantitative analytical technique for tablets with two ingredients. However, if a third or fourth compound is also present, and this contributes to the LRS signal at the frequencies proposed, this could invalidate this approach.

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