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QUANTITATIVE NON-DESTRUCTIVE DETERMINATION OF SALICYLIC ACID ACETATE IN ASPIRIN TABLETS BY RAMAN SPECTROSCOPY

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Summary—Laser Raman spectroscopy was used for the quantitative determination of aspirin in aspirin–maize starch tablets. A calibration curve was constructed from spectra obtained from tablets with known quantities of aspirin and starch. The calibration curve is given from the relationship: $I^{552}/I^{478} = (W_{aspirin}/W_{starch}) \times 4.21$, where I^{552} and I^{478} are the relative Raman intensities for the 552 and 478 cm^{-1} Raman shift, respectively. $W_{aspirin}$ and W_{starch} represent the weight of aspirin and starch in a pellet.

Existing assays for several drugs are time-consuming, especially for routine analysis in a production line. One such case is the determination of the salicylic acid acetate in tablets. The assay consists of hydrolysis of the sample with NaOH and then titration of the excess base with sulphuric acid using phenolphthalein as indicator.[1] The development of a fast and reliable quantitative method is desirable.

In the present work laser Raman spectroscopy (LRS) was used for the qualitative as well as quantitative non-destructive determination of aspirin in a tablet from a spectrum obtained from it. Since there is a vast array of excipients and every manufacturer uses his own 'recipe', a general approach will be described here which can be adapted to virtually any commercially available aspirin tablet. The method was tested with home-made tablets of aspirin and maize starch, a widely used excipient. For this purpose a calibration curve was constructed using the spectra which were obtained from pellets with known quantities of aspirin and maize starch.

EXPERIMENTAL

Pure aspirin and maize starch were donated by Minerva Pharmaceutics, SA, and Boehringer Ingelhaim, Hellas, respectively.

In order to construct a calibration curve, mixtures in the correct stoichiometric ratios were prepared, by mixing aspirin and starch in a marble mortar. The powders were dried at 80°C for 24 hr prior to use. The mixtures were pressed to tablets using a standard IR pellet press. The homogeneity of the pellets was verified by obtaining several spectra from different points on the surface of each pellet.

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 analyzed with a SPEX 1403, 0.85-m double monochromator equipped with a −20°C cooled RCA photomultiplier and EG&G/ORTEC electronic amplifier using photon-counting. The power of the incident laser beam was about 100 mW distributed over the surface of the sample. Typical spectral width and time constant were 1 cm^{-1} and 3 sec, respectively. The system was interfaced with a computer, and spectra were recorded on X-T recorder paper and simultaneously digitized and stored in diskettes.

RESULTS AND DISCUSSION

The objective was to find an easy and reliable method to calculate each ingredient's percentage and, therefore, peak heights were used and not integrated intensities of the bands. The

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differences in the measured intensities of the various spectra made it apparent that only relative factors within each spectrum, e.g. ratios of intensities, could be used.

The starch spectrum exhibited two major Raman peaks at 478 and 2920 cm^{-1} (Fig. 1A). Unfortunately, the latter coincides with an aspirin peak (Fig. 1B) and thus cannot be used. On the other hand aspirin offers a number of well defined Raman peaks. The 552 cm^{-1} peak was chosen because of its proximity to starch's 478 cm^{-1} band which allows very slow scans with large time constants in a reasonable time. Also, the 552 cm^{-1} peak exhibits characteristics similar to those of starch and thus the comparison of their relative intensities was easier.

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, $I(v)$, can be represented as:[2]

$$I(v) = I_0 G(v) C, \tag{1}$$

where I_0 is the intensity of the excitation laser line, v is the Raman shift, $G(v)$ is a 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.

Since $C = W/MW$, where W is the weight of a substance and MW its molecular weight, then a ratio of the intensity of the 552 cm^{-1} aspirin peak to the intensity of the 478 cm^{-1} starch peak can be represented as:

$$\frac{I^{552}}{I^{478}} = \frac{K^{552}}{K^{478}} \frac{W_{\text{aspirin}}}{W_{\text{starch}}}, \tag{2}$$

where I^{552} and I^{478} represents the intensity of the 552 and 478 cm^{-1} peaks, respectively. K^{552} and K^{478} are constants, for the respective Raman shifts, which include the $G(v)$ factor of equation (1) and the MW of each substance.

A plot of the ratios of I^{552}/I^{478} *vs.* the $W_{\text{aspirin}}/W_{\text{starch}}$ ratio yielded a straight line (Fig. 2). The equation for the calibration line was obtained by weighted linear regression, in order to 'force' an intercept of zero:

$$\frac{I^{552}}{I^{480}} = \frac{W_{\text{aspirin}}}{W_{\text{starch}}} 4.21. \tag{3}$$

The correlation coefficient was 0.9996 while the standard errors for the slope and the intercept were $\pm 4.0 \times 10^{-2}$ and $\pm 8.6 \times 10^{-2}$, respectively. The coefficients of variation (CV), which represent the percentage of the relative standard deviation, were also calculated (Table 1) from the four Raman spectra which were recorded for each composition. The value of both intensities was obtained by subtracting the 'background' intensity. Typical aspirin–starch spectra with different $W_{\text{aspirin}}/W_{\text{starch}}$ ratios are shown in Fig. 3.

An increase in the 'background' of the spectra was found to be proportional to the quantity of starch in the pellet. This phenomenon is due to fluorescence arising either from starch itself or from fluorescing impurities in the starch. Fortu-

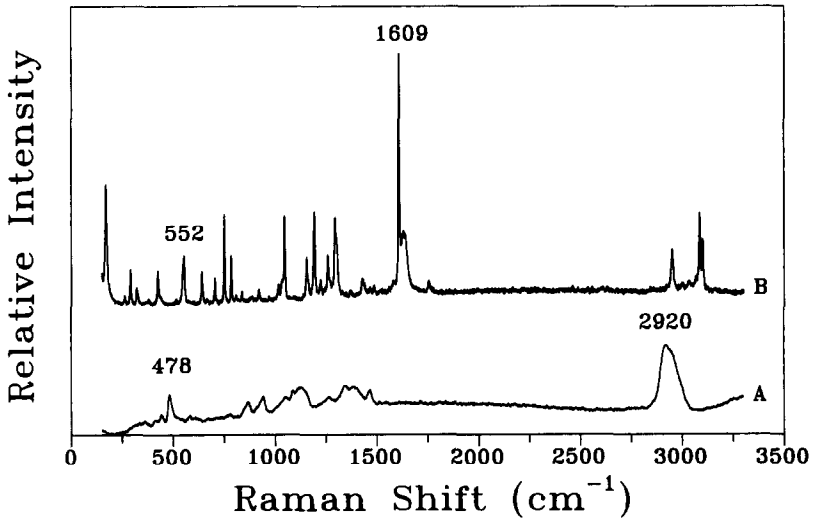

Fig. 1. Raman spectra of tablets from (A) maize starch; (B) pure aspirin. Spectra were excited at 20°C; $\lambda_0 = 488.0$ nm; spectral slit width, 1 cm^{-1}.

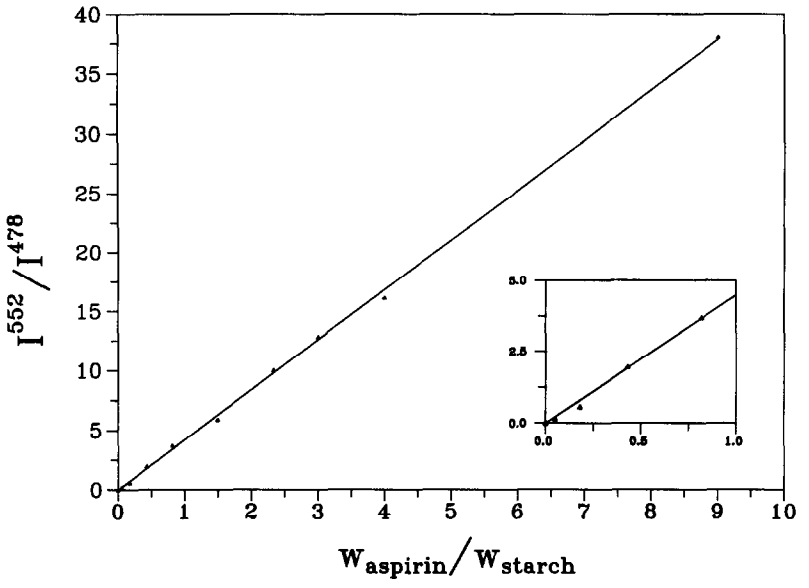

Fig. 2. Calibration line for the determination of the weight ratio of aspirin *vs.* starch in an aspirin tablet.

nately, this did not hamper a determination of the accurate $W_{aspirin}/W_{starch}$.

In the range of our spectral measurements the overall spectrometer response can be considered constant and thus the K ratio is dependent only on the scattering parameter associated with each band. Consequently, the value assigned to the K ratio can be used regardless of the Raman spectrometric system.

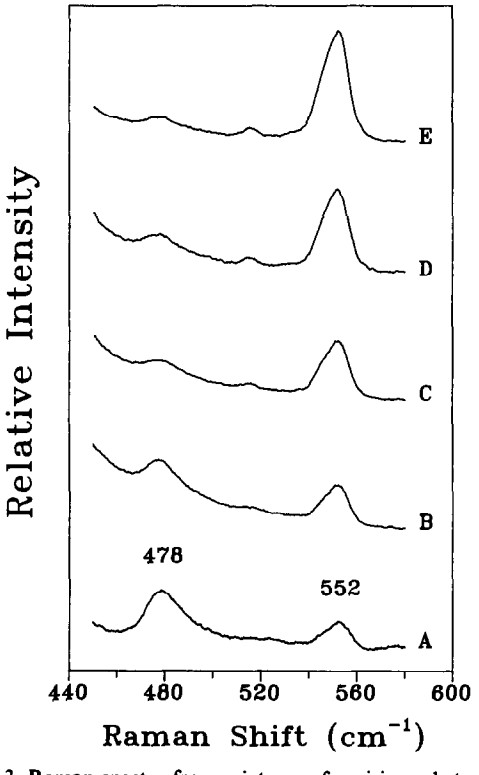

Fig. 3. Raman spectra from mixtures of aspirin and starch in a weight ratio, $W_{aspirin}/W_{starch}$, of A:0.176; B:0.428; C:0.818; D:1.50; E:3.0. Spectra were excited at 20°C; $\lambda_0 = 488.0$ nm; spectral slit width, 1 cm^{-1}.

Table 1. Average ratios of the Raman intensity at 552 cm^{-1} to the Raman intensity at 480 cm^{-1} for aspirin–starch pellets

$W_{aspirin}/W_{starch}$	I^{552}/I^{478}	Coefficient of variation
0.053	0.14	6.2
0.176	0.57	5.2
0.428	1.95	5.4
0.818	3.69	5.3
1.50	5.90	4.8
3.00	12.81	4.3
4.00	16.10	5.1
9.0	38.08	5.7

CONCLUSIONS

A calibration curve for calculating the weight of aspirin in aspirin–starch tablets was developed using Raman spectroscopy. A plot of the intensity ratio of the 552 cm^{-1} peak to the 478 cm^{-1} peak against the weight ratio of aspirin to starch was found to yield a straight line. LRS demonstrates clearly its potential as a non-destructive quantitative analytical technique for tablets with two ingredients. The method is in principle adaptable to any commercially made aspirin tablets.

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