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Raman spectroscopic measurement of tablet-to-tablet coating variability

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Abstract

We report new results suggesting the feasibility of Raman spectrometry as a tool by which to examine the variability of tablet coatings. Our experiments feature a probe that can operate with a revolving laser focus to average content and coating non-uniformity. Raman spectral changes are correlated with tablet exposure times in a pan coater by means of partial least squares (PLS) multivariate analysis. Statistical models are found to be improved by pre-processing schemes that emphasize spectral changes while minimizing the effects of background light scattering and fluorescence. These pre-processing techniques include multiplicative scatter correction (MSC) and standard normal variate (SNV) transformation, used in concert with Savitzky–Golay second derivative smoothing (SGSD). The two approaches give comparable results yielding R^2 values for PLS calibration and cross-calibrated prediction variance regression of 0.999 and 0.997, respectively. Correlation results and model residual values demonstrate that Raman spectroscopy serves sensitively to reflect the coating thickness of the tablets studied.

Keywords: Raman spectroscopy; Tablet coating; Process analysis; Process control; Multivariate classification

1. Introduction

Both pharmaceutical and nutritional solid dosage forms commonly use film coatings. Such membranes offer advantages, both to the consumer and to the pharmaceutical manufacturer. Among the most important are the controlled release of the active pharmaceutical ingredient (API) and the durability of the dosage form in production and on the shelf. In addition, coatings can serve to reduce irritation associated with the exposure of the stomach to high concentrations of medication, and increase product acceptance by improving the visual appeal of a tablet while easing its swallowability and enhancing its taste and odor.

Dissolution and bioavailability are two critical and regulated parameters of any pharmaceutical solid product. These parameters are evaluated for coatings by means of integrity and uniformity analysis. A number of instrumental methods have received substantial attention as potential means for coating process monitoring. Laser-induced breakdown spectroscopy (LIBS) is one such technique, given particular consideration for the study of coating thickness uniformity [1,2]. The main drawback of this approach is its destructive nature. Near infrared spectroscopy (NIR) has also been employed, mainly for coating quantification, where sensitivity to tablet-to-tablet variations in coating amounts has been observed [3–5].

The direct measurement of coating thickness is not an easy task, in part because coating agents are often found unequally distributed over a tablet surface. Indeed, the study of coating variation has been suggested as a diagnostic tool for understanding coating processes and guiding production design to improve product performance and reliability [6].

The present study introduces Raman spectroscopy with multivariate calibration as a potential method to character-

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ize tablet coating thickness and uniformity. We investigate in particular, whether the capacity of Raman scattering to register the fundamental vibrational spectrum of a sample offers advantages for the qualitative assessment of tablet coatings, when compared with the information derived from overtones by NIR.

Our measurements correlate measured Raman spectra with coating times for a large, systematically prepared set of samples. We perform this correlation using the multivariate regression method, partial least squares (PLS). This method functions in general to create a model capable of predicting a set of dependent variables *Y*, on the basis of an independent set of variables *X* [7]. In the case of our study these variables consist of coating exposure times in minutes and Raman spectra, respectively. We use a comprehensive training set of 90 tablets to calibrate a best multivariate representation for each coating time. Our model is designed to fully span the dependent variable range targeted for prediction. Our algorithm employs a non-linear iterative partial least squares (NIPALS) decomposition, wherein a set of latent variables is calculated using the covariance between the dependent and independent variables. This method aims to capture variance while recognizing correlation in the *Y* and *X* data block, thereby constructing an optimally compact predictive relationship between the dependent and independent variables [8,9]. Our work has found strong correlations between matrices describing coating exposure times and Raman spectra. We demonstrate the utility of this correlation for predicting coating times, which suggests that Raman spectroscopy combined with appropriate data pre-treatment and multivariate analysis offers potential as an effective alternative tool for tablet coating analysis.

2. Experimental

2.1. Materials

Tablet ingredients: sulfanilamide (Purum, 98.0%; FLUKA, Buchs SG, Switzerland and Riedel-de Haën, Seelze, Germany), microcrystalline cellulose (Avicel^{TM} PH-200 NF; FMC, Newark, DE), lactose anhydrous for direct compression (Sheffield Brand Lactose NF; Quest International, Chicago, IL), and magnesium stearate (Witco Corporation, Houston, TX) were sieved through a #30 US standard sieve to make the directly compressible formulation for the tablets.

All tablet ingredients were blended in a tote bin blender. Tablets containing 30% (w/w) microcrystalline cellulose, 50% (w/w) lactose anhydrous, 20% (w/w) sulfanilamide and 0.2% (w/w) of total weight magnesium stearate were compressed with a 7/16 in. standard round concave punch to a target weight of 480 mg on a Stokes 16-station B2 tablet press (FJ Stokes Machine Company, Philadelphia, PA).

Coating solution ingredients: hydroxypropyl methylcellulose (HPMC, Methocel^{TM} E3 grade; Dow Chemical Company, Midland, MI), polyethylene glycol 6000 (USP/EP; Dow Chemical Company, Midland, MI) were used as received.

This aqueous coating solution was prepared to consist of 10% (w/w) hydroxypropyl methylcellulose and 1% (w/w) polyethylene glycol. The polyethylene glycol was added to 7 l of 60 °C distilled water. After polyethylene glycol was dissolved, hydroxypropyl methylcellulose was slowly added and the solution was mixed for 20 min to fully disperse the polymer. The solution was removed from the heat and allowed to sit for at least 12 h before use to assure complete hydration of the polymer.

2.2. Apparatus and software

The spontaneous Raman spectra were acquired using an adjustable probe illustrated by Fig. 1, which is connected by a 5 m fiber-optic umbilical to a mobile console (RP-Identification System, SpectraCode Inc. Purdue Research Park West Lafayette, IN). This probe is equipped to revolve the focal spot of the laser that serves to promote Raman scattering from a representative area of the tablet surface. A 1.2 W

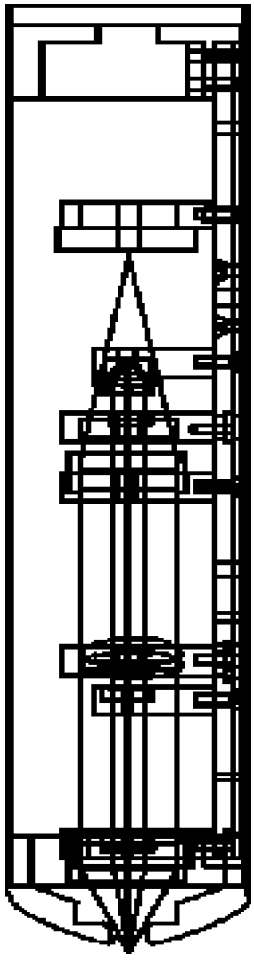

Fig. 1. Raman probe equipped to revolve the focus of the sample illumination and collect backscattered light.

Table 1
Variation of PLS calibration and prediction with data pre-treatment

Data pre-treatment	Raw data	SG second derivative	MCS	SNV	MCS–SG second derivative	SNV–SG second derivative
Number of latent variables	2	2	3	3	2	2
RMSEC (min)	5.56	4.29	6.12	6.12	2.83	2.82
RMSEP (min)	8.24	5.46	7.50	7.50	3.96	3.95

fiber-coupled diode laser provides the excitation source and the probe head employs holographic optics to collect and filter the scattered radiation. We used an exposure time of 1 s. The 5 mm depth of field of this instrument eliminates the need for precise tablet alignment. We averaged 20 spectra per coating exposure time (batch), 180 spectra in all serve to define the PLS regression models.

Multivariate Raman spectral data models correlating spectra with coating exposure times were constructed using a commercial chemometrics software package (The Unscrambler 7.6 SR-1, Camo Technologies, Woodbridge, NJ) and verified by means of PLS_Toolbox 3.0 (Eigenvector Research Incorporated Manson, WA). Data pre-processing was carried out using Microsoft Excel 2000 (MSC and SNV) and Camo Technologies Unscrambler (SGSD).

3. Results

Averaged Raman spectra of tablets subjected to different coating times do not show readily discernable patterns that relate in a directly correlated fashion to the coating exposure time. One challenge to visual interpretation is the irregular nature and varying magnitude of a small baseline contribution to our spectra. This variation, which also interferes with the construction of accurate PLS models, calls for a pre-treatment of the data that includes a transformation to correct for baseline shifts. We tested several pre-treatment approaches including: multiplicative scatter correction (MSC), standard normal variate (SNV) transformation, Savitzky–Golay second derivative (SGSD) smoothing and the combinations MSC–SGSD and SNV–SGSD. These pre-treatments were applied to spectra for the whole Raman shift interval (395–2347 cm^{-1}).

Because baseline shifts arise from the broad effects of background light scattering and fluorescence, both MSC and SNV pre-treatments served effectively to uniformize scans. Accordingly, these two correlation models yield similar root mean square error of calibration (RMSEC) and root mean error of prediction (RMSEP) results using the same number of latent variables, see Table 1.

Both pre-processing techniques gave good baseline corrections and appreciable covariant pattern relationships linking Raman spectral features with the coating exposure time, as can be seen in Fig. 2. The RMSEC and RMSEP values for these pre-treatments were 6.12 and 7.50 min, respectively, with correlations (R^2) of 0.993 and 0.990 for calibration and prediction models. Both models used three latent variables.

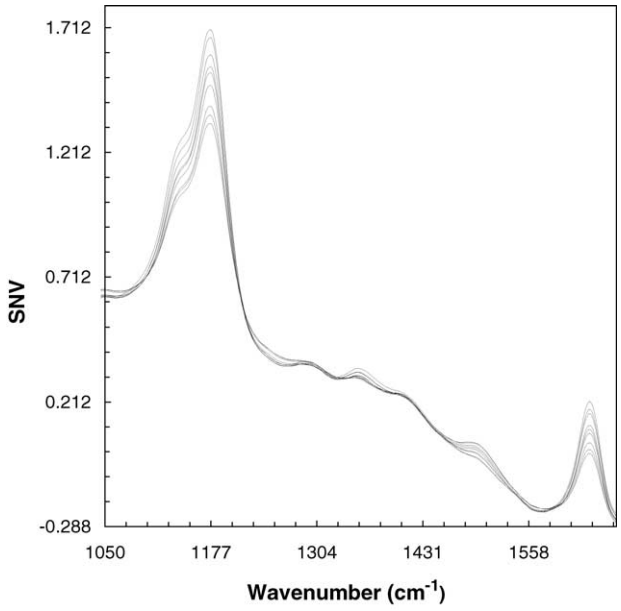

Fig. 2. Region of the SNV pre-processed spectrum of coated sulfanilamide tablets showing the most prominent Raman shift regions, including ring-stretch and symmetric SO_2 stretch from the API at 1630 and 1177 cm^{-1}, respectively, and the aliphatic ether deformation from the HPMC coating polymer at 1480 cm^{-1}. In the spectral region of the sulfanilamide, traces reading from top to bottom correspond to coating times of 0, 20, 40, 60, 68, 100, 120, 145 and 160 min. The Raman intensity in this region decreases as the coating time is increased. Conversely in the HPMC polymer coating region the intensity of the Raman peaks increases in proportion to the coating exposure time.

These models were further improved by the application of SGSD pre-processing with an 11-pixel (56 cm^{-1}) moving window, regressing to a cubic polynomial. This treatment gave SNV–SGSD results of RMSEC and RMSEP of 2.82 and 3.95 min, respectively and correlations (R^2) of 0.999 and 0.997 for calibration and prediction models using two latent variables. For MSC–SGSD the RMSEC and RMSEP were almost identical to the MSC–SGSD, 2.83 and 3.96 min. The R^2 values were the same as for SNV–SGSD pre-treatment, also constructed using two latent variables.

4. Discussion

4.1. Variation of spectral features with tablet coating time

By close examination of loadings derived from our MSC and SNV models we have been able to find spectral areas that

are most closely correlated with the coating exposure time of the tablets. These characteristic Raman shift regions include: the ring stretch and symmetric SO_2 stretch from the API sulfanilamide at 1630 and 1177 cm^{-1}, respectively, and the aliphatic ether deformation associated with the HPMC coating polymer at 1480 cm^{-1}. In the spectral regions corresponding to sulfanilamide, the Raman intensity decreased as the coating time increased. Conversely, in the HPMC polymer-coating region we see a Raman intensity that increases in proportion to the coating exposure time (Fig. 2).

4.2. Data pre-processing

The data processing MSC algorithm compares spectra associated with each different coating time to an ideal spectrum that is constructed from the average of all spectra and adopted as reference [10,11]. To apply this correction to a given spectrum, one plots experimental amplitudes against their values in the reference spectrum. Least-squares regression then determines a characteristic slope (m_i) and ordinate intercept (b_i) for each spectrum. These parameters are used to transform the raw data, Y_{data}, to its corrected form (MCS_{data}) as follows:

$$MCS_{data} = \frac{Y_{data} - b_i}{m_i}$$

As can be seen above, this transformation employs multiplicative m_i and additive b_i effect corrections [12]. This simple mathematical operation thus effectively corrects both offset and proportional baseline shifts in our raw Raman spectra. Such shifts could be expected to arise from background light scattering and sample fluorescence.

The SNV algorithm uses a different approach, although intended for the same purpose [13]. This method does not require an average spectrum like MSC, but rather mean-centers the data for each spectrum and then in each case divides it by the spectral standard deviation. This transforms the data for each spectrum into a waveform that varies around a zero mean emphasizing its spectral changes and scaling it to a unit variance:

$$SNV_{data} = \frac{Y_{data} - Y_{average}}{Y_{STDEV}}$$

Each spectrum baseline is thus shifted and corrected individually without reference to the sample set as a whole.

Spectra, baseline corrected by either the MCS or SNV approach yield a subtle but discernable relationship between tablet coating time and Raman feature amplitudes. Further application of Savitzky–Golay second derivative smoothing better emphasizes these spectral changes, and thus can be expected to offer a higher spectral variation. We performed MCS–SGSD, SNV–SGSD and SGSD transformations using the 5-pixel full width at half-maximum (FWHM) of the sulfanilamide ring stretch (1630 cm^{-1}) peak. The moving average or filter width was calculated to be twice the FWHM of this peak [14] for a total 11 pixels, or about 56 cm^{-1} (Fig. 3).

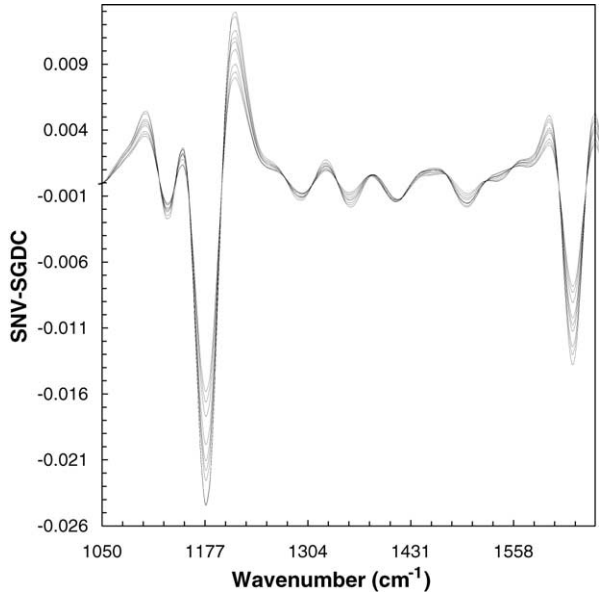

Fig. 3. Representative spectra following Savitzky–Golay smoothing and double-differentiation applied as a pre-treatment to the SNV data. This data treatment emphasizes feature changes in the SNV Raman spectra. The moving average for pre-treatment is 11 pixels (ca. 56 cm^{-1}).

Using this moving average, SNV–SGSD gives the lowest RMSEC and RMSEP for the PLS calibration, as illustrated in Figs. 4 and 5. MSC–SGSD gives almost identical values. But, it can be argued that the simplicity of SNV algorithm, which corrects each spectrum separately instead of using the whole training set, as does MSC, makes the former more attractive as a pre-processing strategy.

The *Y*-residuals of both models demonstrate a good description of all samples. The normal probability plots of residuals for the MSC–SGSD and SNV–SGSD indicate no outliers, and no systematic error in the measurements, confirm-

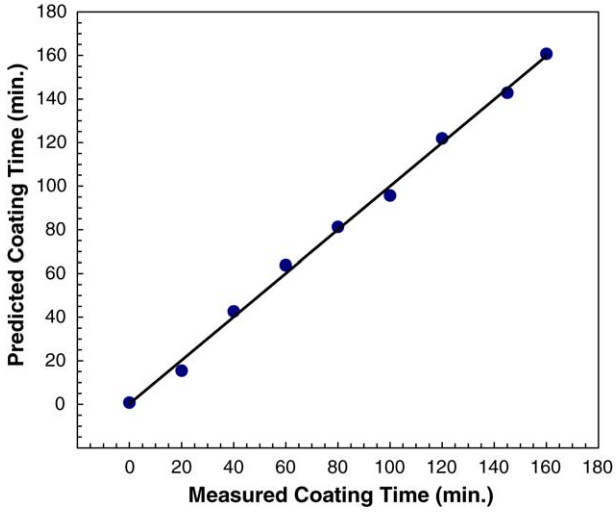

Fig. 4. Calibration variance regression model results for SNV–SGSD. This model gives a RMSEC of 2.82 min using two latent variables.

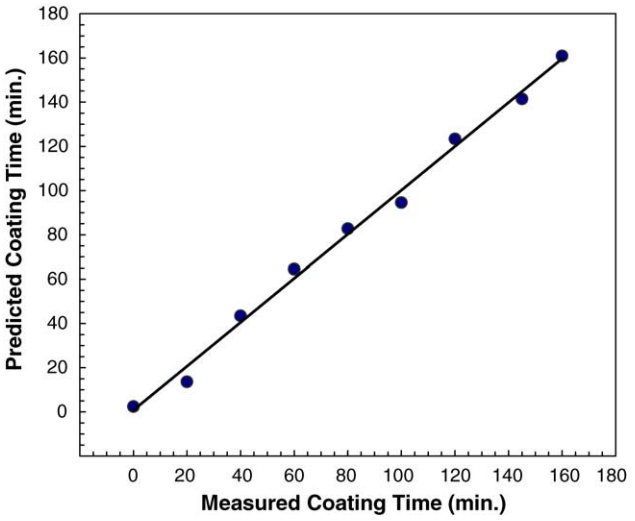

Fig. 5. Cross calibrated prediction variance regression model results for SNV–SGSD using two latent variables. The RMSEP value for this model is 3.95 min.

Table 2
Example calculated tablet coating variations from nominal values

Test sample nominal coating time (min)	Predicted coating time (min)	Deviation (min)
0	−9.934	−9.934
20	20.092	0.092
40	39.129	−0.871
60	72.701	12.701
80	90.211	10.211
100	99.907	−0.093
120	123.393	3.393
145	139.718	−5.282
160	159.934	−0.066

ing the suitability of these data pre-processing schemes for PLS model creation.

Using PLS regression results to construct predictive models, one could investigate the variability of tablet-to-tablet coating thickness in production by introducing new samples and characterizing their deviations in terms of the model. As an example, the prediction value for one sample of each coating time was calculated using the SNV–SGSD model. This analysis was carried with the same tablets used to calibrate because more samples were not available (Table 2). This test should not be confused with an evaluation of our coating process.

5. Conclusions

Raman spectroscopy using a revolving laser focus combined with PLS multivariate spectrochemical analysis appears to offer a simple and robust technique by which to quantitatively characterize coating variations. An important factor in this study is the benefit of a moving laser focus, which increases the sampling area and thus yields a measurement more likely to reflect the real composition of the sample. Raman spectroscopy like NIR offers the advantages of minimal sample preparation and no sample destruction. It is non-invasive and readily capable to use as a remote sampling analytical tool by means of fiber optical probes.

This approach is readily expandable to correlate Raman spectra with coating concentrations, sample weight increments and tablet disintegration times, as well as separately measured coating thickness. Work along these lines is underway.

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