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Comparative study of non-destructive methods to quantify thickness of tablet coatings

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ABSTRACT

The Supercell coater is a newly introduced coater which utilizes air fluidization for tablet coating. The aim of this study was to define a suitable, fast and non-destructive method for the quantification of coat thickness for Supercell-coated tablets. Various coat thickness characterization methods were carried out on tablets coated at different process conditions. These include the use of optical microscopy, micrometer, X-ray fluorescence (XRF), Raman and near-infrared (NIR) spectroscopy. Coat thicknesses obtained from direct measurements were used to calibrate the spectral data from spectroscopic methods for model generation. The models were subsequently validated to evaluate their prediction capabilities, especially the ability to differentiate tablets coated at different conditions. XRF spectroscopy was viewed to be more suitable for the assessment of process yield and efficiency but both Raman and NIR spectroscopy were shown to be more appropriate methods for the rapid prediction and evaluation of coat thickness. However, only Raman spectroscopy was able to differentiate tablets coated under different conditions accurately. In conclusion, direct thickness measurements were more time-consuming but provided assured coat thickness data. On the other hand, XRF, Raman and NIR spectroscopy methods were viable alternatives to provide complementary information for the study of tablet coatings.

1. Introduction

Film coating is an important unit process associated with the manufacture of many solid dosage forms. It serves to impart numerous advantages to a dosage form. These include the masking of unpleasant taste or odor, stability enhancement, aesthetic improvement and modifying of drug release profiles. For consumers, coating of medications allows ease of identification and improves swallowability. For manufacturers, coating can help to reduce dust and improve the mechanical strength of tablets to withstand handling. Coating also provides a form of branding for marketing purposes, thus allowing the product to stand out from competition (Cole, 1995). Traditionally, tablets are coated using pan coaters. In pan-coating, tablets rotate in a uniformly perforated cylindrical drum while the coating dispersion is sprayed with drying air supplied co-currently. The Supercell coater (GEA Pharma Systems, UK) is a recent introduction for tablet coating. Its mode of action is based on the use of fluidizing air for tablet coating, which had typically been of limited interest due to the severe attrition caused to tablets (Porter, 2007). In the Supercell coater, the air distribution plate is specially altered to reduce the impact that fluidization air has on the tablets. The reduction in tablet damage once again opened up the possibility of tablet coating using air fluidization techniques.

The thickness and uniformity of film coatings provide information on the quality of film coated tablets. Film coated tablets should display an even coverage of film over the whole tablet surface (Hogan, 1995). Direct measurement of coat thickness is seldom carried out and the use of theoretical or indirect thickness measurements is often preferred. A recent proposal for direct coat thickness measurement utilized an ultrasonic wave pulse to determine coat thickness based on time-of-flight measurements of the elastic wave propagation in the coating layer (Akseli et al., 2009). However, other direct thickness measurement methods remain in general, a laborious procedure which is also prone to errors. For this reason, the development of a quick, non-destructive and accurate method for measuring coat thickness was explored in several studies. A pharmaceutical process, such as film coating, is a complex multivariate system. Multivariate measurement methods like Raman (Kauffman et al., 2007) or near-infrared (NIR) spectroscopy (Buchanan et al., 1996; Perez-Ramos et al., 2005) use a single measured data to carry the information on the property to be evaluated. Other methods which are also used for analysis of coated tablets include acoustics (Akseli and Cetinkaya, 2008), terahertz spectroscopy (Ho et al., 2007), X-ray photoelectron spectroscopy (Felton and Perry, 2002), Fourier transform infrared spectroscopy (Felton and Perry, 2002) and laser-induced breakdown spectroscopy (Madamba et al., 2007). Although the concept of relating such techniques to the coat

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Table 1
Physical characteristics of tablets used for coating.

Parameter	Value
Weight	121.0 ± 1.3 mg
Diameter	6.040 ± 0.004 mm
Thickness	4.210 ± 0.021 mm
Hardness	45.5 ± 6.7 N
Surface roughness (Ra)	582. 1 ± 191.6 nm
Color	L = 96.08 ± 0.58, a = −0.41 ± 0.38, b = 3.71 ± 0.26

Note: *L*, *a*, *b* refer to *CIELab* units (Commission Internationale d'Eclairage, France).

thickness of coated tablets is not new, it was of additional interest to evaluate the sensitivity of these methods to determine differences in coat thickness as a result of changes to processing conditions in the Supercell coater. Moreover, no study had attempted to compare several spectroscopic methods to evaluate the most suitable method for future analysis of film coated tablets.

In this study, the usefulness of Raman, NIR and X-ray fluorescence (XRF) spectroscopy as methods for coat thickness determination were assessed. The main objective of this study was to identify a suitable, fast and non-destructive method for future quantification of coat thickness for Supercell-coated tablets. By predicting coat thickness accurately using information from such process analyzers and incorporating them in manufacturing process controls, it will help ensure optimal performance of the final product.

2. Materials and methods

2.1. Core tablet characterization

Normal circular biconvex tablets (6 mm diameter) made by direct compression were used for coating. Tablet core composition consisted of lactose, microcrystalline cellulose, starch and polyvinylpyrrolidone. Tablet weight (AG-135, Mettler Toledo, Switzerland), thickness and diameter (293-761-30, Mitutoyo, Japan), hardness (HT-1, Sotax, Switzerland), surface roughness (Wyko NT1100, Veeco Instruments, USA) and color (Chroma Meter CR-241, Minolta, Japan) were determined. Ten randomly selected tablets were used for each test and results averaged. Table 1 gives the average values of the tablet characteristics.

2.2. Coating dispersion

The 15% (w/w) solids coating dispersion applied was composed of 12% (w/w) hypromellose (Methocel-E3, Dow Chemicals, USA), 2% (w/w) polyethylene glycol (PEG3000, BASF, Germany), and 1% (w/w) iron oxide (Red 30, BASF, Germany) in water.

2.3. Experimental design

It was hypothesized that tablet load and plenum pressure contributed the most to the flow kinetics of tablets in the Supercell coating process. Hence, a factorial design was used to vary the levels of tablet load (L) and plenum pressure (P). This study was a 2^2 full-factorial design with two factors at two levels of process parameter settings (high and low). The high and low levels of process parameter settings for tablet load and plenum pressure were 50 and 100 g, and 1500 and 1800 mmWC, respectively. Four different process conditions were investigated. They were denoted as *lp*, *Lp*, *lP* and *LP*. Capitalized letters indicate coating carried out at the high levels of process parameter settings while non-capitalized letters indicate coating carried out at the low levels of process parameter settings. Tablets were coated to six different coating levels, namely, 0.4, 0.8, 1.2, 1.6, 2 and 3% (w/w) theoretical weight gain. Theoretical weight gain was defined as the theoretical increase in dry weight of tablets after coating. The coating runs were duplicated.

2.4. Coating process and parameters

Coating was performed using the Supercell coater according to the recipes as stipulated by the full-factorial design. Coating dispersion was delivered at a spray rate of 8 mL/min, with an atomizing pressure of 3 bars and an inlet temperature of 100 °C. After a short period of drying, the coating cycle was completed and the tablets were automatically discharged by pneumatic conveyance out of the processing chamber.

2.5. Measurement of coat thickness

From each coated tablet batch, eight tablets were randomly selected and cut diametrically into halves using a sharp blade. Tablet cross-sections were examined under a stereomicroscope (BX61, Olympus, Japan) under 40× magnification, with the cut surface facing up. Images were captured with a digital color video camera (DXC-390P, Sony, Japan) and coat thickness was measured with the aid of an image analysis software (MicroImage version 4.5, Media Cybernetics, USA). Thickness of coat was measured at twelve pre-determined locations around the tablet cross-section (Fig. 1A). At each location, the thickness of the coats at five closely spaced points in the locality were measured and averaged to give a more accurate determination of coat thickness at that particular location. Thickness of the coat (t) was defined as the perpendicular distance between the edge of the substrate core and the edge of the coat. The average coat thickness of each tablet was given by the average of thickness measurements at all twelve locations. Coat thicknesses of tablets were also determined using a micrometer screw gauge (293-761-30, Mitutoyo, Japan). Diameters of at least 5 tablets were measured and averaged. Coat thickness was defined as half the dimensional difference between coated and uncoated tablets.

2.6. X-ray fluorescence (XRF) spectroscopy

XRF spectroscopy was carried out using the X-ray analytical microscope (XGT-7000V, Horiba Scientific, Japan). Scanning of tablet surface was carried out using a 100 μm diameter laser beam. Each tablet was analyzed for its element content at three locations on the tablet face and five tablets from each batch were scanned. Element peaks were automatically located and labeled, allowing quantitative analysis of element content to be carried out. As the coat formula used contained iron oxide as colorant, iron was the element of interest during analysis. The amount of iron present on the tablet coat should theoretically correlate with the amount of coating applied on the tablet surface.

2.7. Raman spectroscopy

Acquisition of Raman spectra was carried out using a Raman spectrometer (R3000, Raman Systems Inc., USA). A diode laser of excitation wavelength 785 nm was used in this system, which provides a very stable excitation with high signal to noise ratio. Each tablet was placed in a sample holder on a mounting stage at the focal distance of the probe and scanned on both surfaces using a beam size of 300 μm. On each tablet face, three different locations were scanned and three tablets were analyzed from each processing batch.

2.8. Near-infrared (NIR) spectroscopy

NIR spectra were acquired using an NIR fiber optic fluorescence probe (QR600-7, Ocean Optics, USA), which has an effective beam diameter of 600 μm. The probe was attached to a separate NIR

source and sensor (MCS 611 NIR 2.2, Carl Zeiss, Germany). Ten tablets were scanned on both faces from every processing batch.

2.9. Model development

Coat thickness measurements obtained from direct optical microscopy from the first replicate runs of *lp*, *lP*, *Lp* and *LP* were used as the reference values for quantitative calibration and model development. All spectroscopic analyses were carried out in a non-destructive manner. A total of 450 Raman spectra, 500 NIR spectra and 375 X-ray spectra were used for calibration. This corresponded to 18, 20 and 15 spectra for every coating condition at each coating level for Raman, NIR and X-ray fluorescence spectroscopy, respectively. The average spectrum of these spectra was used for model development. The spectral regions used for both Raman and NIR spectroscopy were between 1000–1900 cm^{-1} and 1000–1900 nm, respectively. Using experimentally designed data from a full-factorial study for calibration, it ensured that the calibration set covered the X-space in a representative manner. The duplicate runs of all batches were subsequently used as validation batches.

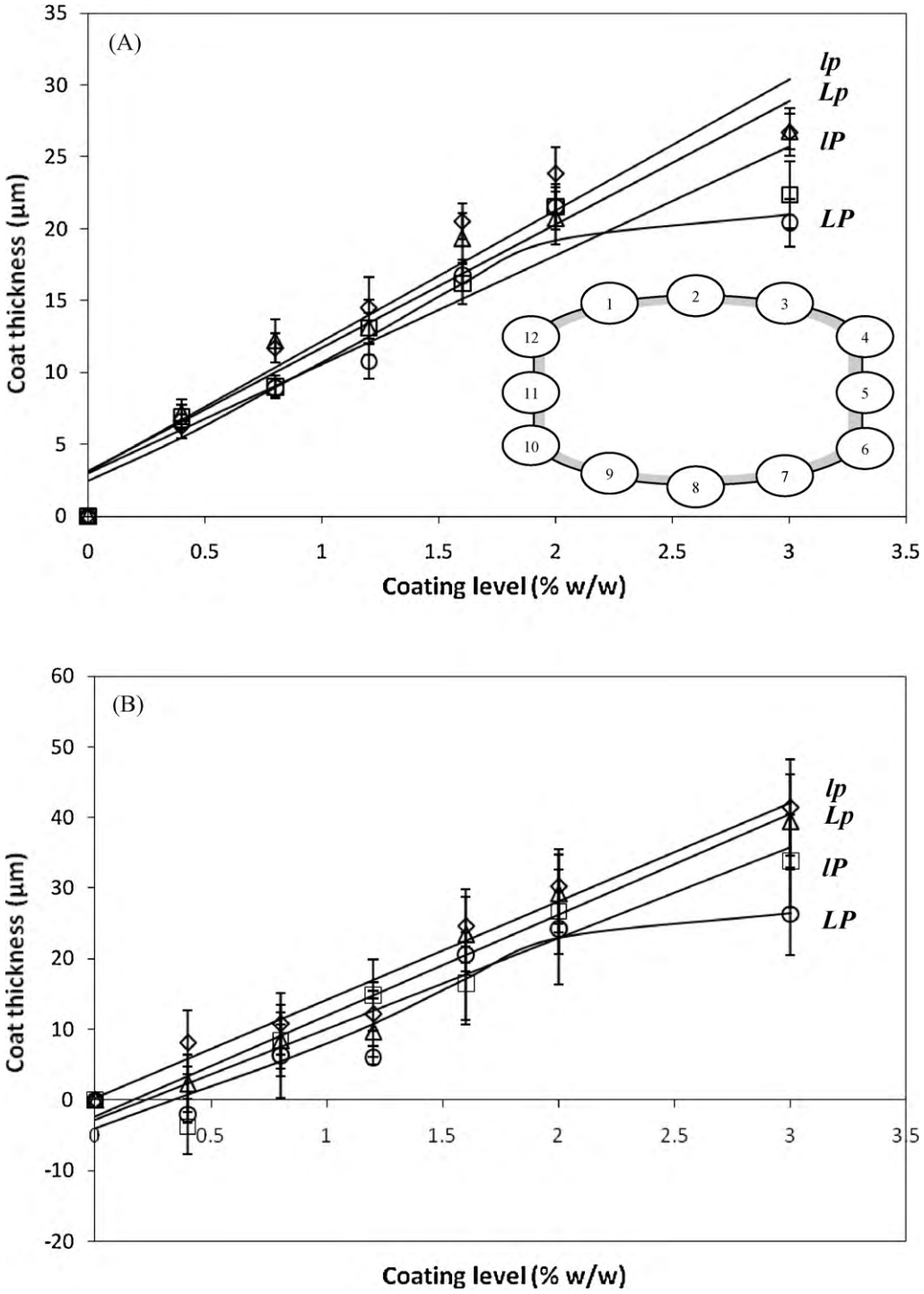

Fig. 1. Relationship of coat thickness and coating level for tablets coated at *lp* (◊), *lP* (□), *Lp* (△) and *LP* (○) as measured using (A) direct microscopy and (B) micrometer methods. (A) Insert: an illustration of the twelve locations around the tablet cross-section where thickness measurements were obtained. Five measurements were made at each location and values averaged.

The coat formula used in this study contained hypromellose which has a prominent Raman shift at approximately 1480 cm^{-1} where aliphatic ether deformation of the polymer occurs (Romero-Torres et al., 2005). It was expected that as coating level increased, the thickness of the tablet coat increased and this would be proportional to the content of hypromellose present in the tablet coat. Some characteristic NIR vibrations for hypromellose include CH, CH_2 and CH_3 vibrations at 1200 and 1700 nm, and R–OH vibrations at 1450, 1900 and 2100 nm (Lin-Vien et al., 1991). For both Raman and NIR spectra processing, smoothing of the spectra was first performed using Sarvitzky–Golay smoothing. Spectra were also pre-processed using the Standard Normal Variate (SNV) algorithm. In this transformation, scattering is removed by normalizing each spectrum by the standard deviation of the responses across the entire spectral range ($SNV_{data} = (Y_{data} - Y_{average})/Y_{sd}$). Partial least squares regression (PLS1) was used as the regression method whereby dependent variable Y can be predicted on the basis of independent variable X. For all spectral processing and chemometric analyses, the Unscrambler version 9.8 (Camo, Norway) was used.

3. Results and discussion

3.1. Thickness measurements analysis

Fig. 1A shows the relationship between coat thickness and coating level when direct optical microscopy was used as the measurement method. Fig. 1B shows the relationship between coat thicknesses measured using the micrometer screw gauge and coating level. Coat thickness was shown to increase as coating level increased for tablets coated at all conditions with the exception of *LP*, where a leveling effect was observed when the coating level exceeded 2% weight gain. For the other 3 coating conditions, linear regression resulted in squared correlation coefficients (R^2) of more than 0.9. This leveling effect was postulated to be due to a reduction in the coating process efficiency of coating at *LP*. The results shown in Section 3.2 confirmed this hypothesis. Tablet load, plenum pressure and the interaction effect between them were not shown to be statistically significant in affecting coat thickness for all coating conditions at all coating levels tested. This result was not necessarily discouraging as the lack of difference between tablets coated at different conditions suggests that the Supercell process was sufficiently robust within the experimental design space and changes to tablet load or plenum pressure would not affect coat thickness to any significant extent.

For coat thickness determination using the micrometer screw gauge, the tablet central band was selected as the measurement region. As the face of the tablet experienced a greater amount of elastic recovery after compaction, the variability of tablet height was much greater than the variability of tablet diameter. Since coat thickness was defined by the dimensional difference between coated tablets and average dimension of uncoated tablets, the use of tablet diameter measurements would minimize the inaccuracies in coat thickness approximations. Although this method lacked sensitivity at the lower coating levels, it still gave reasonable trend accuracy at higher coating levels even though measurement errors were much larger. Also, the coat thickness values obtained using the micrometer were consistently higher than those determined by optical microscopy. This was probably due to the micrometer's insensitivity and invariable over-estimation in measurements close to the micron range. Regardless of the inadequacies of the method, the use of the micrometer remains as one of the most popular methods of coat thickness measurement because measurements are rapid and non-destructive, and the micrometer is affordable. It should be noted that there was generally good agreement between the thickness measurements obtained using both the micrometer and the optical microscopy method. At 3% (w/w) coating weight gain, the coat thickness of tablets coated at various process conditions in the Supercell coater showed a trend, decreasing in the order of *lp* > *Lp* > *lP* > *LP*.

Direct method of thickness measurements such as optical microscopy was often considered too laborious. However, vibrational spectroscopic methods like Raman or NIR spectroscopy can measure many simultaneous chemical and physical parameters indirectly. XRF spectroscopy is also useful to detect the elemental content of the tablet coat. These methods are advantageous as they are reasonably rapid, non-destructive and allow the representative sampling of more dosage units. In this study, these methods were evaluated comparatively as analytical tools for evaluating the Supercell-coated tablets. Coat thickness was chosen to be correlated to the spectroscopic techniques because the variation in coat thickness would likely reflect a corresponding change in the analytical signal. When combined with chemometric methods, such spectroscopic measurements allow the prediction of coat thickness with the use of appropriate calibration models. Thus, a method for the rapid evaluation of the applied coating and its uniformity during the coating process may be developed. In a coating process, coat thickness can vary greatly on the face and side of the tablet. However, in this study, no significant difference was observed between the coat thickness at the face and side of the tablet. Therefore, the data obtained from the various analytical techniques were calibrated using the average coat thickness obtained from direct measurements at all locations of the tablet. Even though direct coat thickness measurements were time-consuming, they provided assured and reasonably accurate results for spectra calibration and model generation.

3.2. X-ray fluorescence (XRF) spectroscopy

The inclusion of an active drug to the coating formulation and the subsequent detection of this active compound on the tablet coat have been traditionally used as one of the methods to evaluate coating uniformity. However, it is often not the formulator's intention to incorporate actives into the coat unless there is interest in using the coating process for layering of the drug in a coat-dosing system. Moreover, the addition of actives into the coating formula might unintentionally alter the properties of the coat. Typically, iron oxide pigments are incorporated into the coating formulation as colorants. It is therefore possible to evaluate coat uniformity based on the distribution of the pigments instead of actives. Thus, it may be feasible to use XRF spectroscopy to assay the amount of iron present in the coat. As iron oxide is usually present in a relatively low proportion, the uniformity of its distribution would also be useful for predicting the thickness of tablet coats. In XRF, X-rays are directed at atoms which excite the electrons located in the internal orbit of the electron shell, causing them to move to the outer shells. When the electrons fall back to the vacant orbit, X-rays equivalent to the energy difference between the orbits are generated. This X-ray fluorescence generated is specific to each element and is detected by the silicon semiconductor detector. It is possible to detect the fluorescence released as a result of iron present in the tablet coat and this would be proportional to the amount of coating applied.

Elemental analyses of materials often require the use of atomic absorbance spectroscopy. However, atomic absorbance spectroscopy is a wet-chemistry based analytical method which is both time-consuming and destructive. There has been no literature report on the use of XRF spectroscopy to investigate tablet coats. Laser-induced breakdown spectroscopy was successfully used to detect emissions of iron in coated samples (Madamba et al., 2007). However, the method is a destructive method as a high-power laser is used to ablate the surface of the sample. This allows the sample to dissociate into its atomic species, which are subsequently excited.

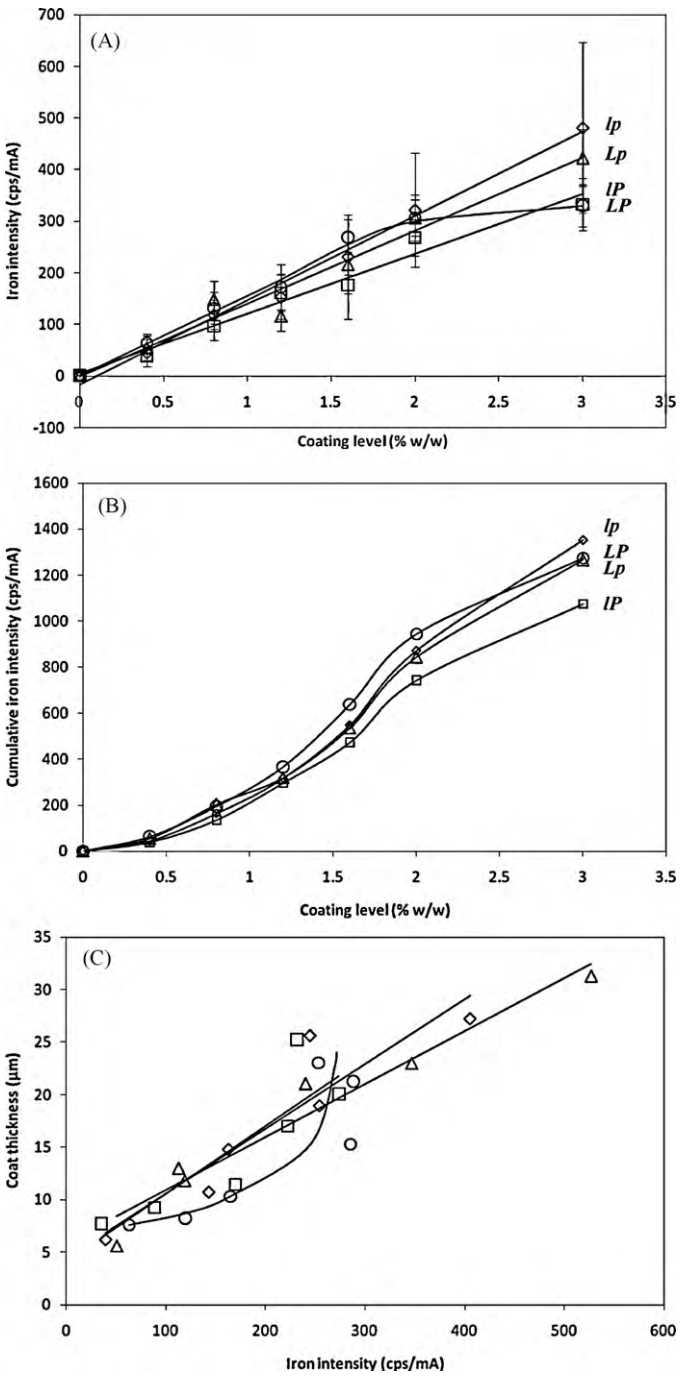

Fig. 2. Tablets coated at conditions of *lp* (◊), *lP* (□), *Lp* (△) and *LP* (○) to 0.4, 0.8, 1.2, 1.6, 2 and 3% (w/w) coating weight gain. The amount of iron present on the tablet coat was analyzed using X-ray fluorescence spectroscopy. (A) Relationship between the intensity of iron detected from the coat surface and the coating level. (B) Cumulative curve for the increase in iron intensity with increase in coating level. (C) Relationship between coat thickness and iron intensity.

Similar to XRF spectroscopy, the atoms would emit light at wavelengths characteristic of the elements present during the relaxation phase.

Fig. 2A shows the relationship between iron count rate detected by the XRF spectrometer and coating level. It was observed that the iron content present in the tablet coat was generally closely related to coat thickness. However, a difference was observed for tablets coated at *LP* at the lower coating levels of less than 2% weight gain. In previous coat thickness characterization tests, tablets coated at *LP* consistently showed thinner coats compared to those coated at *lp* and *Lp*. On the contrary, results from XRF spectroscopy showed that iron content was higher for tablets coated at *LP* until the leveling effect was observed. Coat thickness was a measured outcome which may be affected by process conditions. For instance, increased air entrapment between the polymer layers would increase coat thickness although the amount of coating applied was kept constant. Hence, the amount of iron present on the tablet coat could instead act as a reflection of the process efficiency and need not be related to coat thickness. The leveling effect observed here was an indication that process efficiency was declining over time with less coating materials deposited. Process efficiency was defined as the amount of coating materials applied to the tablets, which was indicative of the amount of iron deposited. Since the application rate of the coating dispersion onto tablets during the coating process was constant, the greater the amount of iron deposited at any time indicated better efficiency of the process at that condition. The cumulative curve for iron intensity as shown in Fig. 2B shows that tablets coated at *LP* did not actually have the lowest process efficiency because there was a high iron deposition rate at the earlier stages. However, there was a decline in the successful rate of coat application in *LP* as the coating process progressed. The visibly decreased coater efficiency under *LP* at 3% (w/w) coating level represented significant depression of coater's efficiency under a high load coupled with high plenum pressure. This was likely to be due to a disruption to the flow dynamics in the coating chamber when coating level increased. It was postulated that as tablet weights increased, the tablets preferred to remain closer to the walls of the coating chamber. As the spray nozzle is located in the centre of the air distribution plate, increased spray drying of coating materials might have occurred since a plug flow of fluidizing air was present. This effect was intensified in *LP* due to a high tablet load and plenum pressure employed during the coating run.

Calibration of iron intensity against coat thickness could easily be performed without the use of chemometric instruments since there was only one element of interest. This was carried out by calibrating coat thickness obtained from direct optical microscopy against the iron intensity (Fig. 2C). For coat thickness to be directly correlated to iron intensity, a linear relationship should be observed between the two variables. However, the trend lines observed were chaotic and relationship between the two parameters was not directly predictable. In this study, coat thickness was not suitably calibrated against iron intensity. Good linear relationship was only observed for tablets coated at *Lp*. However, for tablets coated at *LP*, the same leveling effect was observed and there was no increase in iron intensity with increasing coat thickness or coating level. As only the data from the first replicate of the coating runs were used for calibration, this calibration model would probably improve when the sample size was increased. For instance, from Fig. 2A, which included the average data from all coating runs, clear and accurate distinction between the iron intensity and coating level of tablets coated at different conditions were observed at 3% (w/w) coating weight gain.

Although XRF spectroscopy might be useful as a method for coat thickness calibration and prediction, iron intensity was not always be directly related to coat thickness. It was felt that XRF spectroscopy had greater utility in providing additional information to the coating process such as quantifying the efficiency of the coating process. However, it was shown to be useful for rapidly quantifying the amount of coating applied onto the tablet surface by detecting the iron pigments present in the coat formulation. This method utilizes the surface analysis of materials, which therefore makes it an extremely valuable tool for the study of tablet coatings and its associated variability. With the advancement of tablet coating technologies, it might be possible to accurately deposit low-dose actives on the tablet coat, thereby circumventing the granulation step usually undertaken to ensure eventual dose uniformity of actives in all

the tablets. XRF spectroscopy could rapidly assay the amount of actives present on the tablet coat and replace the use of traditional wet-chemistry methods. This method would be feasible when the molecular structure of the actives contains elemental groups which could be detected by XRF spectroscopy.

3.3. Raman spectroscopic prediction of coat thickness

Raman spectroscopy has found many applications in the pharmaceutical industry, ranging from detection of counterfeits to determination of active contents (Sasic, 2007). The current popular pursuit is the possible application of Raman for process manufacturing as a process analytical technology (PAT) tool for good process control. Raman spectra consist of bands which correspond to vibrations of the molecules of interest. Energy is transferred between the excitation source and the molecules with inelastic scattering of monochromic radiation. Advantages of Raman spectroscopy include the non-invasive nature of measurements. It is also fast, with little or no sample preparation.

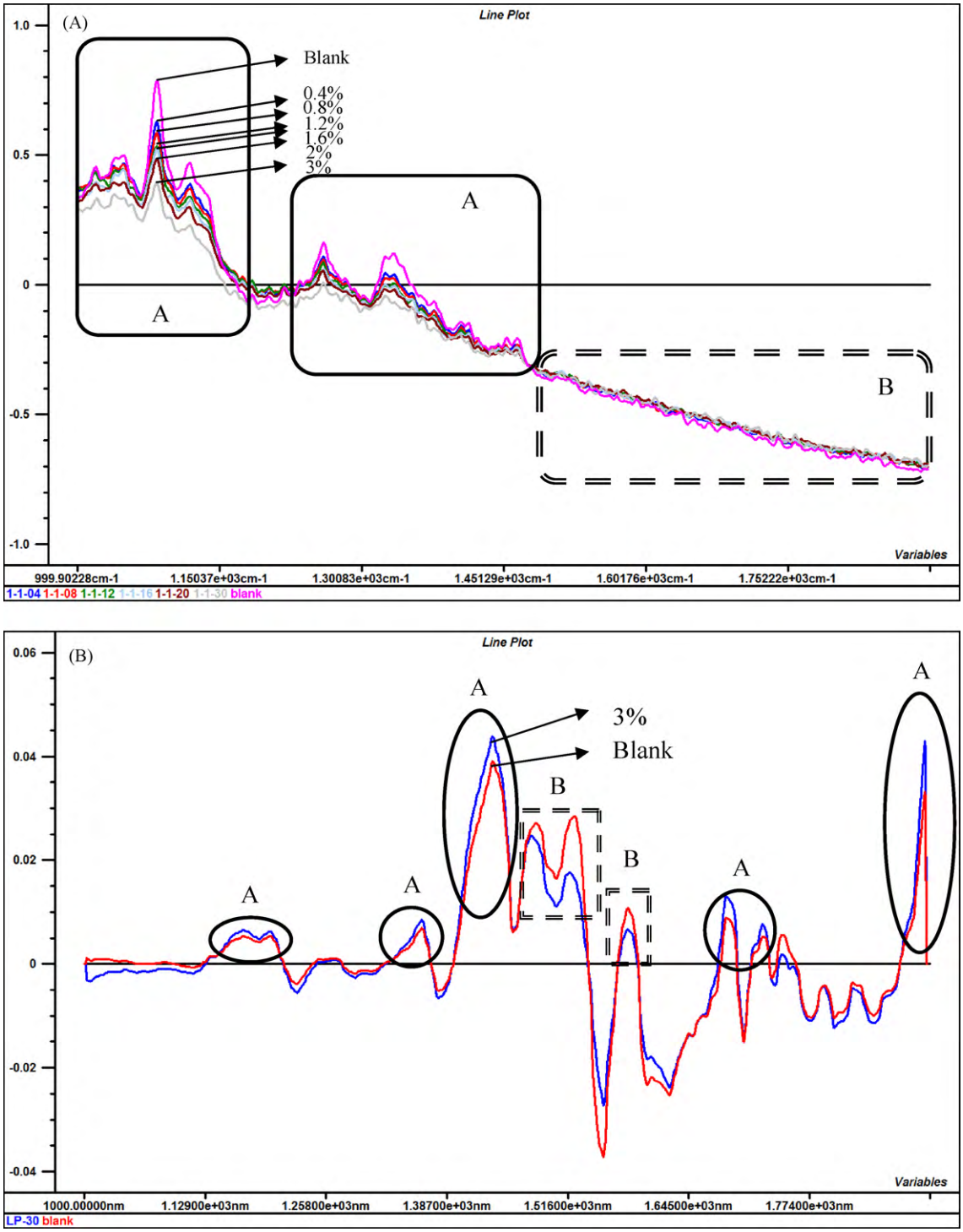

Fig. 3. (A) Raw Raman spectra of blank tablet core and tablets coated to 0.4, 0.8, 1.2, 1.6, 2 and 3% (w/w) coating weight gain (*LP*). (B) Second-derivative NIR spectra of blank tablet core and tablets with 3% (w/w) coating weight gain (*LP*). *Note*: Region A corresponds to contributions by the tablet core while region B corresponds to contributions by hypromellose. With increasing coating level, the coating's contribution to the analytical signal increases but the contribution due to the tablet core decreases.

Some technical challenges associated with using Raman spectroscopy to quantify tablet coatings are fluorescence, which can be pronounced for colored samples such as those containing iron oxide, and also the lack of analytical specificity due to the overshadowing of much weaker Raman signals (McGoverin et al., 2008). However, it was reported that Raman could be a viable means of non-invasively quantifying tablet coating thickness through the judicious use of several data transformation approaches despite the presence of fluorescent ingredient (Romero-Torres et al., 2006). Moreover, it had also been previously found to be suitably calibrated against coating thickness (Kauffman et al., 2007). A separate study also found it to be a useful method of analysis for tablet-

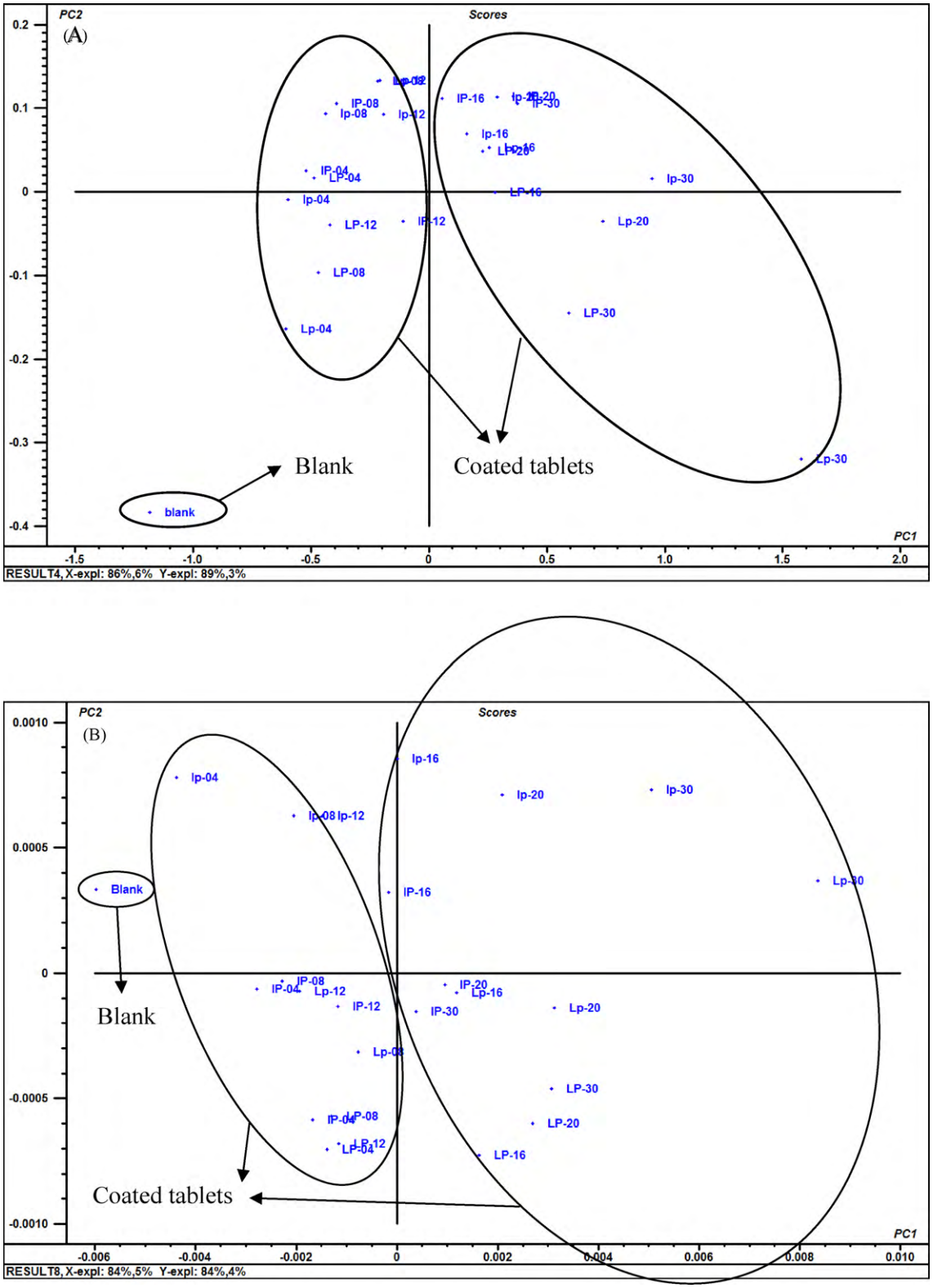

Fig. 4. Scores plot of samples generated from (A) Raman spectra calibration and (B) NIR spectra calibration.

to-tablet variation of coating thickness (Romero-Torres et al., 2005).

In this study, Raman spectra were correlated against changes in coat thickness as coating progresses. As the coating level increased, it was found that the intensity contributions due to the tablet core were reduced but the intensity contributions due to the coating increased (Fig. 3A). In a paper by Kauffman et al. (2007) the total analytical signal was assumed to be a linear combination of coating and core signals. Therefore, partial least squares (PLS) regression method was used to relate the Raman spectra obtained with coat thickness in this study.

Calibration was performed on spectra obtained from tablets coated during the first runs of all coating conditions tested and also thickness measurements obtained from optical microscopy. They made up the calibration and training sets, respectively. Full cross-validation was used to generate the calibration model, and test set validation was performed on the model subsequently. From the scores plot for calibration samples (Fig. 4A), it was possible to

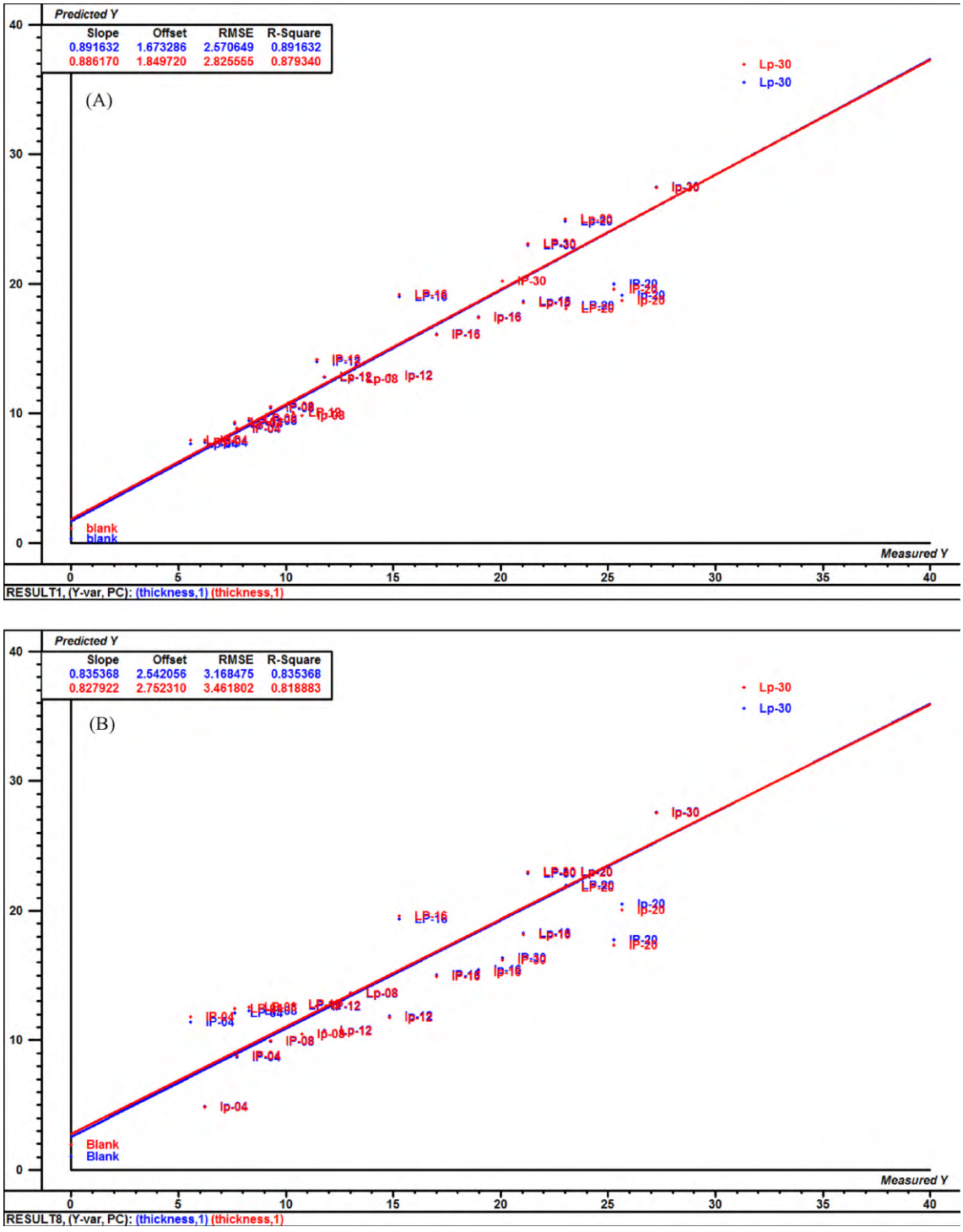

Fig. 5. Summary of PLS1 calibration model built using (A) pretreated Raman spectra at the 1000–1900 cm^{-1} region and (B) pretreated NIR spectra at the 1000–1900 nm region.

Table 2
Comparison between (A) Raman-predicted and (B) NIR-predicted coat thickness values with measured values for tablets coated at various coating conditions.

Coating level (%, w/w)	*lp*		*lP*		*Lp*		*LP*	
	Coat thickness (μm)							
	Predicted (SD)	Measured (SD)	Predicted (SD)	Measured (SD)	Predicted (SD)	Measured (SD)	Predicted (SD)	Measured (SD)
(A) Raman-predicted coat thickness values								
0	0.38 (1.54)	0 (0)	0.38 (1.54)	0 (0)	0.38 (1.54)	0 (0)	0.38 (1.54)	0(0)
0.4	9.24 (1.64)	6.27 (0.92)	7.09 (1.85)	6.15(0.66)	8.26 (1.68)	8.77 (1.35)	6.17 (1.67)	5.59 (1.13)
0.8	11.01 (1.79)	12.64 (0.98)	11.11 (1.58)	8.73 (0.80)	13.66 (2.06)	11.43 (1.24)	11.22 (2.01)	9.63 (0.54)
1.2	14.72 (2.33)	14.20 (1.95)	12.32 (5.17)	14.75 (1.02)	12.17 (2.05)	14.45 (1.97)	9.00 (2.34)	11.25 (1.47)
1.6	15.96 (3.58)	22.08 (0.79)	12.22 (2.11)	15.40 (1.18)	15.42 (2.12)	17.60 (1.13)	17.59 (3.50)	18.22 (1.34)
2	20.76 (1.76)	22.08 (1.91)	19.90 (2.76)	18.28 (1.26)	20.09 (2.73)	18.47 (1.99)	23.58 (1.77)	20.01 (1.24)
3	31.67 (2.62)	26.26 (1.63)	27.95 (3.49)	24.76 (2.33)	22.77 (2.25)	21.45 (1.48)	22.18 (1.44)	19.01 (1.41)
Mean	14.82	14.79	13.00	12.58	13.25	13.17	12.87	11.96
(B) NIR-predicted coat thickness values								
0	1.02 (11.20)	0 (0)	1.02 (11.20)	0 (0)	1.02 (11.20)	0 (0)	1.02 (11.20)	0 (0)
0.4	9.99 (5.74)	6.27 (0.92)	9.80 (5.23)	6.15 (0.66)	8.30 (7.29)	8.77 (1.35)	9.76 (4.70)	5.59 (1.13)
0.8	12.22 (6.21)	12.64 (0.98)	12.70 (4.38)	8.73 (0.80)	12.73 (3.59)	11.43 (1.24)	14.99 (4.10)	9.63 (0.54)
1.2	15.40 (2.91)	14.20 (1.95)	15.24 (5.17)	14.75 (1.02)	11.67 (4.28)	14.45 (1.97)	10.75 (3.93)	11.25 (1.47)
1.6	15.48 (5.35)	22.08 (0.79)	14.51 (4.05)	15.40 (1.18)	20.04 (4.26)	17.60 (1.13)	14.94 (5.10)	18.22 (1.34)
2	20.51 (4.39)	22.08 (1.91)	18.67 (5.36)	18.28 (1.26)	22.49 (3.68)	18.47 (1.99)	21.79 (4.96)	20.01 (1.24)
3	26.14 (5.18)	26.26 (1.63)	26.26 (5.18)	24.76 (2.33)	35.57 (4.66)	21.45 (1.48)	21.09 (5.10)	19.01 (1.41)
Mean	14.39	14.79	14.03	12.58	15.97	13.17	13.48	11.96

differentiate clusters of coated samples as well as blank tablets. The closer the samples are in the score plot, the more similar they are with respect to the two components concerned. Conversely, samples far away from each other are different from each other. Unfortunately, it appeared that tablets coated to different coating levels were not very effectively clustered. However, general clustering was observed for blank tablets, tablets coated up to 1.2% (w/w) coating level and lastly, tablets coated between 1.6 and 3% (w/w) coating levels. Percentages of *X* and *Y* explanations were also shown on the scores plot. If the sum of the explained variances for the two PLS components were large, it indicates that the plot shows a large portion of the information in the data and relationships may be interpreted with higher degrees of certainty. On the other hand if it is small, it might be necessary to study more components, to consider another transformation or there might just be too little meaningful information in the data. The scores plot generated from this study resulted in high *X* and *Y* explanations (both 92%) for the first two PLS components. Fig. 5A shows the PLS1 calibration model generated. Only one PLS component was required to explain the variation between *X* and *Y*. RMSEC (root mean square error of calibration = 2.57) was found to be close to RMSEP (root mean square error of prediction = 2.83). This meant that prediction error was low since the deviations between predicted and real values were rather low. Calibration was successfully performed with an R^2 value of 0.89 while the R^2 for prediction was found to be 0.88.

The calibration model was validated using Raman spectra and thickness measurements obtained from the duplicate runs of *lp*, *Lp*, *lP* and *LP*. Independent sample *t*-test was used to compare the means between Raman-predicted and optically measured thickness values, and *p*-values greater than 0.05 indicate no statistical significance between measured and Raman-predicted coat thickness. A list of Raman-predicted values and its corresponding measured values are shown in Table 2A. For all conditions tested, no significant difference was found between measured and Raman values, which meant that the model was successful in predicting the coat thickness of the coated tablets. As spectroscopic methods often have high levels of error, it might be useful to further increase sampling sizes to improve the model as well as the prediction abilities. However, general visual inspection showed that similar trends were observed (Fig. 6A) when compared to direct microscope measured thickness measurements. Tablets coated at *lp* had the thickest coat, followed by those coated at *Lp*, *lP* and *LP*. The leveling of coat thickness in *LP* was also successfully predicted. At the lower coating levels, the trend on how thickness was varied did not appear to be distinct between different methods. It was probable that the higher inter-tablet thickness variations at lower coating levels

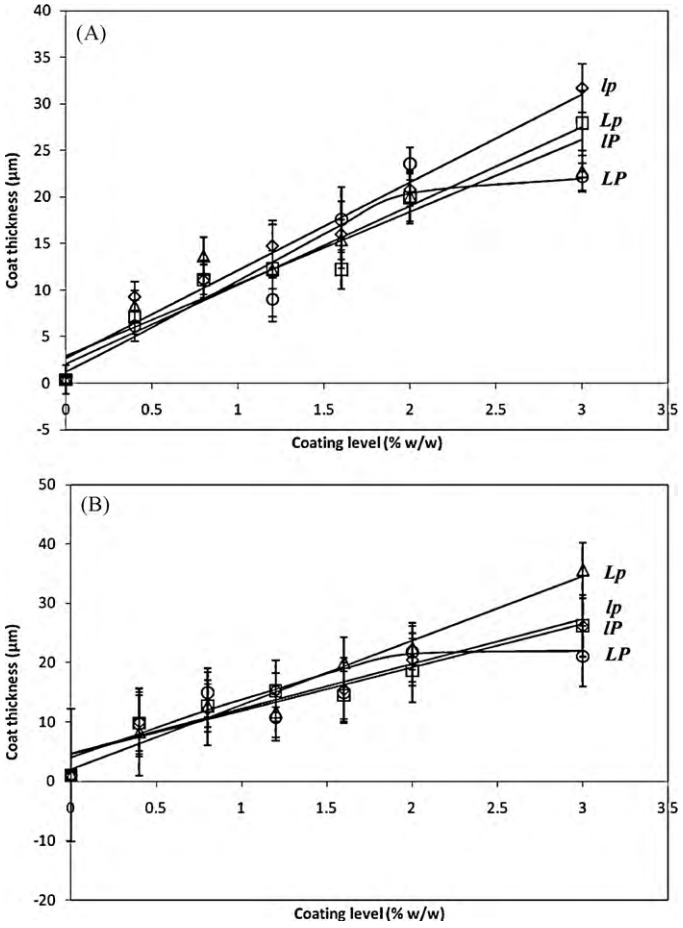

Fig. 6. Relationship between coat thickness and coating level as predicted by (A) Raman and (B) NIR spectroscopy, for tablets coated at *lp* (◊), *lP* (□), *Lp* (△) and *LP* (○).

could have made discrimination more difficult. It was possible to use this model to predict tablet coat thickness for future experiments which utilize the same conditions as those in this study. This method of analyzing tablet coatings would allow many more tablets to be examined than the currently recommended numbers under pharmaceutical suggested guidelines. It may be possible to even screen all coated tablets with a high-speed in-line method.

3.4. Near-infrared (NIR) spectroscopic prediction of coat thickness

Most materials will absorb IR radiation to a certain extent. When a source of IR energy irradiates a sample, the sample will absorb the energy resulting in transitions between molecular vibrational and rotational energy levels. For a fundamental vibrational mode to be IR active, a change in the molecular dipole must take place during the molecular vibration. Typically, anti-symmetric vibrational modes and vibrations due to polar groups are more likely to exhibit prominent IR absorption bands. Absorption bands in the NIR region of the spectrum arise from overtones or combinations of fundamental vibrational motions, in addition to combinations of overtones. Overtone absorption bands are the result of forbidden transitions arising from the ground vibrational energy level to a higher atomic energy level greater than 1. Since overtone bands arise from forbidden transitions, they are typically 10–1000 times less intense than their corresponding fundamental absorption bands (Bugay and Findlay, 2002). However, an advantage of NIR is its ability to penetrate much further into a sample than mid infrared radiation. Therefore, although NIR spectroscopy is not a particularly sensitive technique, it is still very useful for analyzing bulk materials with little or no sample preparation. The majority of overtone bands in the near-IR arise from R–H stretching modes (O–H, N–H, C–H, S–H). Due to the large mass difference between the two atoms, large-amplitude vibrations arise with high anharmonicity and large dipole moments. Typically, in pharmaceutical analysis, NIR spectroscopy is used for the detection of water (strong O–H combination band). The many O–H and O–R (R = CH, CH_2, CH_3) groups present in the structure of hypromellose could possibly contribute to the detection and measurement of applied coatings.

When coating level was increased, it was found that the intensity contributions due to the tablet core were reduced but the intensity contributions due to the coating increased (Fig. 3B). The same clustering pattern was observed from the scores plot of NIR calibration samples (Fig. 4B) as compared to the scores plot of the Raman method. This indicates equivalent clustering capabilities. The scores plot generated from this study resulted in high *X* and *Y* explanations (89 and 88%, respectively) for the first two PLS components. Fig. 5B shows the PLS1 calibration model generated. Only one PLS component was required to explain the variation between *X* and *Y*. RMSEC (root mean square error of calibration = 3.17) was also found to be close to RMSEP (root mean square error of prediction = 3.56). Prediction error was low since the deviations between predicted and real values were low. Calibration was successfully performed with an R^2 value of 0.84 while the R^2 for prediction was found to be 0.82.

The calibration model was validated using NIR spectra and thickness measurements obtained from the duplicate runs of *lp*, *Lp*, *lP* and *LP*. A list of NIR-predicted values and its corresponding measured values are shown in Table 2B. Independent sample *t*-test was used to compare the means between NIR-predicted and measured thickness values. For all conditions tested, no significant differences were found between measured and NIR-predicted values, which meant that the model was generally adequate in predicting the coat thickness. However, it was observed from Fig. 6B that at 3% (w/w) coating level, tablets coated at *Lp* had the thickest coats, followed by those coated at *lp*, *lP* and *LP*. This differed from results obtained previously by all other methods. The validation process had erroneously predicted that tablets coated under *Lp* had thicker coats than *lp*. In general, the standard deviations of coat thickness values associated with the NIR spectroscopic method were also higher compared to the Raman method. In addition, the model generated from NIR spectroscopy also had a relatively lower prediction potential than the Raman model as observed from the R^2 values. However, it should be noted that since coat thickness values between tablets coated under different conditions were not significantly different from one another in the first place, the failure of the NIR model to detect the small difference did not mean that NIR spectroscopy was not a suitable PAT tool for use in process monitoring. On the other hand, it simply meant that it was not as sensitive to pick up the small differences in thickness present in this study but might still be a useful tool for the evaluation of tablet coats under other circumstances.

4. Conclusions

Direct optical microscopy method for cross-sectioned coat thickness measurement was considerably laborious but generally provided accurate coat thickness data. Good approximations of coat thicknesses may also be obtained from the difference between the thickness values of coated and uncoated tablets using the micrometer. Although this method was comparatively less accurate than actual optical microscopic measurements, it was less time-consuming compared to the microscopy method. For the coating condition *LP*, coat thickness was found to level off above 2% (w/w) coating weight gain. This was due to the reduction in the coating process efficiency at *LP*. In this study, a suitable, non-destructive method used for the measurement of coat thickness should therefore be capable of detecting and predicting this non-linearity.

XRF spectroscopy was shown to be a useful tool for rapidly quantifying the amount of coating applied onto the tablet surface by detecting the iron pigments present in the coat formulation. The principle of its operation was based on elemental specificity of compounds when exposed to X-rays and related the fluorescence response to the efficiency of the coating process. However, coat thickness values obtained did not correspond to the amount of iron present on the tablet coats. Although considerable direct correlations were observed, XRF spectroscopy was not viewed to be the most suitable method to quantify and predict coat thickness.

Raman spectroscopy was shown to be a suitable method for the rapid evaluation of tablet coat thickness. The technique was also found to be capable of differentiating tablets coated under different conditions and would be valuable for use as a tool for non-destructive, exhaustive in-line measurement of tablet coat quality. On the other hand, data obtained from NIR spectroscopy did not manage to differentiate coat thicknesses of tablets coated under different conditions as effectively as Raman spectroscopy. However, both Raman and NIR spectroscopy were able to predict the non-linearity of coat thickness in *LP*. NIR is still a promising measurement tool as under different conditions such as different core and coating formulations, more accurate measurements are possible. As the differences found in this study were not marked, NIR spectroscopy appeared to lack the sensitivity to detect the differences present.

XRF, Raman and NIR spectroscopic methods were useful as complementary methods for the study of tablet coating to derive different information. However, in this study, Raman spectroscopy appeared to be the best method for the characterization of tablet coat thickness.

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