Blending uniformity analysis of pharmaceutical powder by near infrared spectroscopy

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Introduction

In the pharmaceutical industry, the powder blending process is one of the most common operations, to mix the Active Pharmaceutical Ingredient (API) with other ingredients uniformly for quality control.[1-5] Recently, Near-infrared (NIR) spectroscopy has become an analytical technique of great interest for the pharmaceutical industry, particularly for the non-destructive analysis of powder blends, to replace high performance liquid chromatography (HPLC) in pharmaceutical process control.[6-10] The purpose of the work to be described was to evaluate the role of NIR spectroscopy in monitoring the composition of pharmaceutical powder blends.

Materials and Methods

Sample preparation

API, disintegrant, lubricant and more ingredients were provided by the Government Pharmaceutical Organisation of Thailand. NIR calibration models were developed and validated for the work, based on a 5-level (%w/w) calibration sample set. Calibration and validation sample sets, each of 125 samples were set up. The samples were prepared by weighing suitable amounts of API, disintegrant, lubricant and other non-APIs into a separate 20 ml bottle. Amounts of ingredients are summarised in Table 1. An analytical balance with precision of ±0.01 mg was used. The total weight for each sample was approximately 5 g. The samples were mixed manually by shaking, and then visually inspected for uniformity, which was later confirmed by the validation process.

Table 1. Designed calibration sample (all numbers are in % weight/weight).

API	Disintegrant	Lubricant	Other non-API
24.88	2.6500	0.6550	to 100%
37.32	3.9750	0.9825	
49.76	5.3000	1.3100	
62.20	6.6250	1.6375	
76.64	7.9500	1.9650	

Spectral acquisition

A NIR spectrophotometer model NIRFlex N400 with 2-m fibre-optic probe (Buchi, Flawil, Switzerland) was used for spectral acquisition. The NIR spectra were measured with Interactance fibre optics in the wavelength region of 4008 cm^{-1} to 9996 cm^{-1}, with a resolution of 12 cm^{-1} interval in reflectance mode. The probe, the depth of which was about 10 mm, was inserted through the adapter cap, and the sample bottle was turned upside down. The powder had to cover the tip of the probe to decrease the variation of NIR scans, as seen in Figures 1 and 2. All samples were recorded by a scanning FT-NIR-spectrometer in random order from 5 locations. Each sample was scanned 5 times. The 5 spectra were averaged for determination of the degree of homogenisation.

Reference analysis

Reference API concentrations were measured with a high performance liquid chromatography instrument model UltiMate 3000 Rapid Separation LC system (Dionex, Germany). The refer-

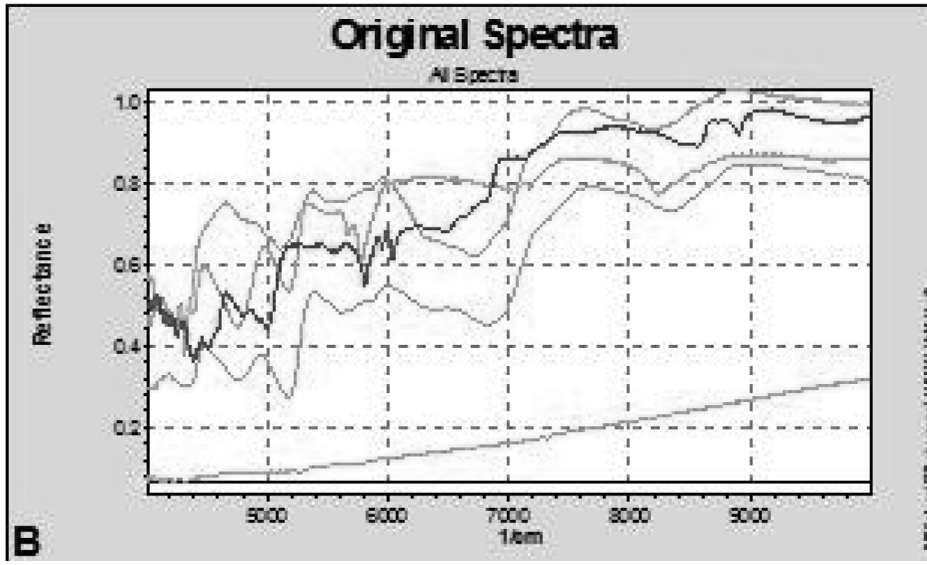

Figure 1. Spectra of API (Bold Line) and Other Ingredients.

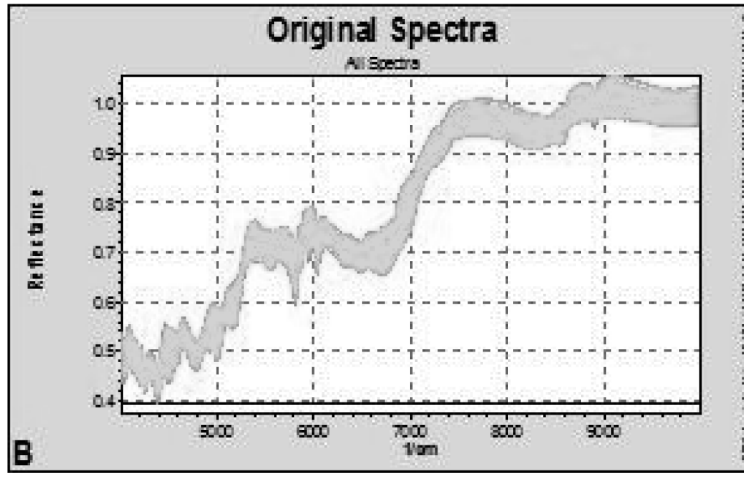

Figure 2. Original Spectra of Samples in Calibration and Validation Sets.

ence method was performed following the United States Pharmacopeia 30. The data were average values, calculated from duplicate measurements.

Results and discussion

Calibration model

The calibration model showed a strong correlation with the reference values and good accuracy. Statistical values including the Standard Error of Calibration (*SEC*), Standard Error of Prediction (*SEP*), Bias and correlation coefficient of determination (R^2) showed the suitability of the calibration model to predict %API and excipients during blending. Table 2 summarises *F*: The number of factors; R^2: the coefficient of multiple determination; *SEC*: standard error of calibration, *SEP*: standard error of prediction; bias (the average of differences between reference value and NIR values); *RPD*: the ratio of standard deviation of reference data in the validation set to *SEP*.

Table 2. PLS calibration results for predicting %API calculated from second derivative NIR spectra, and validation results of NIRS method for powder blending process.

The correlation between true proportions (HPLC method) for %API versus predicted proportions (NIR method) (Figure 3) resulted in high correlation coefficients of 0.9980 for both calibration and validation sets. Accuracy, expressed as the bias in the validation, showed that the robustness and reproducibility of the NIRS model for the determination of %API was high, which demonstrated that the NIR model could be used to predict %API in the blending process.

The validation results of NIR method

The method predicted the %API in the validation set with essentially no bias, and the mean content did not differ from that determined by the HPLC method. Differences in values obtained with the two methods were compared statistically using the paired t-test at the 95% confidence level, (Table 2 and Figure 3).

Table 2. PLS calibration results for predicting %API calculated from second derivative NIR spectra and validation results of NIRS method for powder blending process.

Blending time (minute)	Wavelength region (cm^{-1})	Statistical parameters						Validation results		
								%Label Amount of API		*P*-values
		F	R^2	*SEC*	*SEP*	Bias	*RPD*	NIR	HPLC	
21 minute	4392–4800 5400–6600 7800–9996	8	0.9980	2.26	2.24	0.00	15.74	100.24	100.40	0.2657
22 minute								101.03	100.57	0.2597
23 minute								100.43	100.43	0.8566
24 minute								100.69	100.68	0.7431
25 minute								100.52	100.51	0.6286

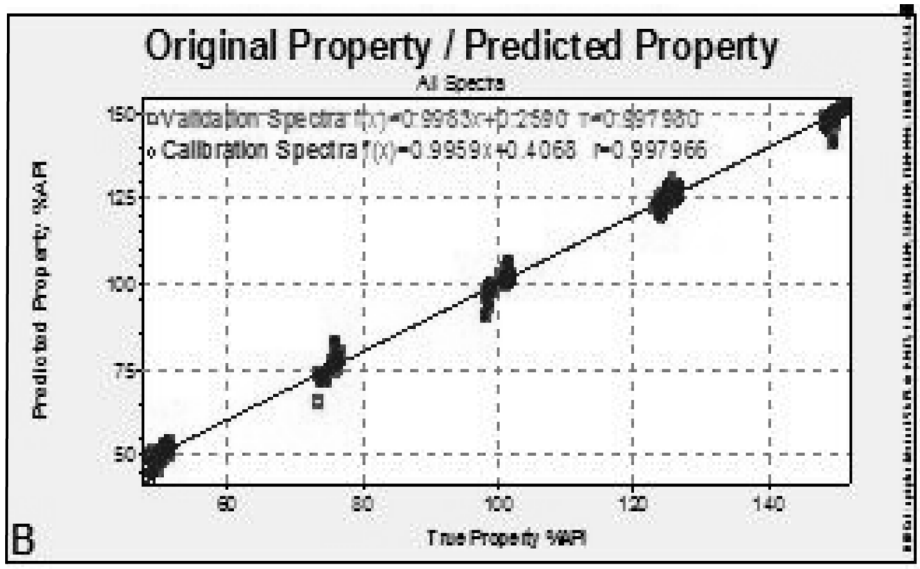

Figure 3. The Correlation between True Propertion and Predicted Propertion of API.

Optimise mixing times of blend homogeneity

The amount of API, as a percentage of the blended powder, was determined by NIR spectroscopy and compared to the amount as determined by HPLC. The blending profile in Figure 4 shows a typical behavior of mixing curves. The mixing time to obtain homogeneity of API in the blended powder was optimised at 20 minutes. The homogeneity index (*%RSD*) was less than 5.0% as specified in the United States Pharmacopeia 30.

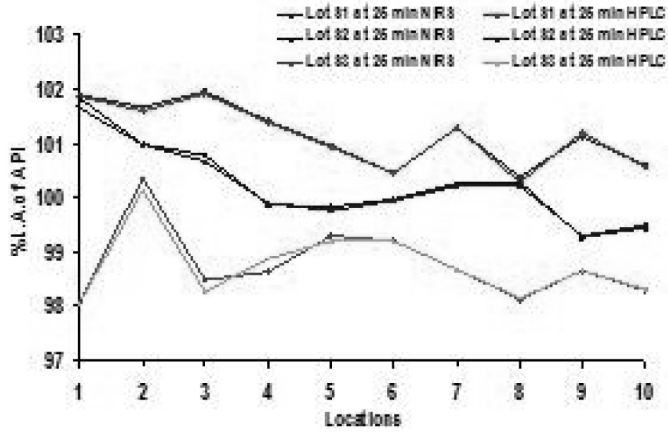

Figure 4. Label amount of %API in blended powders by NIRS method, compared to the HPLC method in lot S1.

Conclusion

The NIR technique was verified as suitable for quantitative analysis of API and exipients in pharmaceutical powder blends, compared with the conventional methods such as HPLC. The NIRS method can provide analytical results with minimum delay. The technique also has potential for optimising mixing times to achieve blend homogeneity. The NIR technique has good potential for applications in product quality assurance, and could benefit the blending step in process control. Because the method requires minimum sample preparation, and does not call for the use of potential environmentally harmful reagents, it could be used to analyse large number of samples during process development, detect drug agglomeration problems, and facilitate process development.

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