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Automated system for the on-line monitoring of powder blending processes using near-infrared spectroscopy Part I. System development and control

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Abstract

An automated system for the on-line monitoring of powder blending processes is described. The system employs near-infrared (NIR) spectroscopy using fibre-optics and a graphical user interface (GUI) developed in the LabVIEW environment. The complete supervisory control and data analysis (SCADA) software controls blender and spectrophotometer operation and performs statistical spectral data analysis in real time. A data analysis routine using standard deviation is described to demonstrate an approach to the real-time determination of blend homogeneity.

Keywords: Near-infrared spectroscopy; On-line analysis; Fibre-optics; Blending; Chemometrics; Pharmaceutical analysis; Process control

1. Introduction

Near-infrared (NIR) spectroscopy is receiving a great deal of attention within the pharmaceutical industry as it offers the pharmaceutical analyst the ability to perform analysis with little or no sample preparation. One application that has created much interest is the use of NIR spectroscopy for blend analysis [1–6]. During the manufacture of a solid dosage form, a critical operation is the blending together of the active component with excipients. The goal of this manufacturing operation is the production of a homogeneous blend that when further processed into individual dosage units yields a high-quality product capable of providing an accurate unit dose. The traditional analytical approach to in-process control blend analysis is shown in Fig. 1a. After a specified time interval, samples are obtained from the blending vessel and submitted to an analytical laboratory, with the appropriate sample submission forms, for analysis. The in-process control blend analysis is

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then performed using chromatographic or spectroscopic techniques in an analytical laboratory that is often remote from the point of manufacture. A report is then issued detailing the analytical results and at this stage a decision is made as to whether to proceed to the next manufacturing process. Laboratory Information Management Systems (LIMS) can do much to streamline this protracted process, but sample turnaround can take a significant amount of time. This delay obviously extends manufacturing times and results in expensive materials and/or equipment lying idle awaiting the analytical results before proceeding to the next manufacturing step. Often manufacturing campaigns are designed to allow for the expected delay between sampling and reporting of the analytical data. This built-in delay results in extended and inefficient production schedules. An alternative philosophy is to gather analytical information in real time at the point of manufacture, and this concept is known as process analytical chemistry (PAC) (Fig. 1b). PAC allows information to be generated from analytical data in real time and any deviation from the process norm elicits an immediate response. PAC generally requires the use of chemometric techniques to obtain meaningful information from the multivariate analytical data obtained from process measurements. These chemometric approaches are often alien to the traditional analytical chemist who is typically used to dealing with univariate or bivariate data. Consequently, the reporting of analytical results obtained from the use of chemometric techniques may raise concerns as the data can often be presented in a non-traditional manner. To illustrate the point, a literature example using 'conformity index' reports results as 'meeting conformance' rather than an absolute quantitative value [7].

PAC techniques applied to blend analysis have yet to be reported. NIR spectroscopy is an excellent tool for process blend analysis as it lends itself to on-line analysis. This paper describes the development of an automated system for blend analysis with online process measurements using NIR spectroscopy. Further chemometric analysis and approaches to the exploitation of the information generated by an on-line NIR system will be described in further publications in this series. A patent for the automated system has been filed for its use [8].

2. Experimental

2.1. Near-infrared spectrophotometer

NIR spectra were collected using a NIRSystems 6500 spectrophotometer (NIRSystems, Silver Spring, MD, USA) configured with a reflectance fibre-optic probe. The scan range employed was 1100–2500 nm and each spectrum was the average

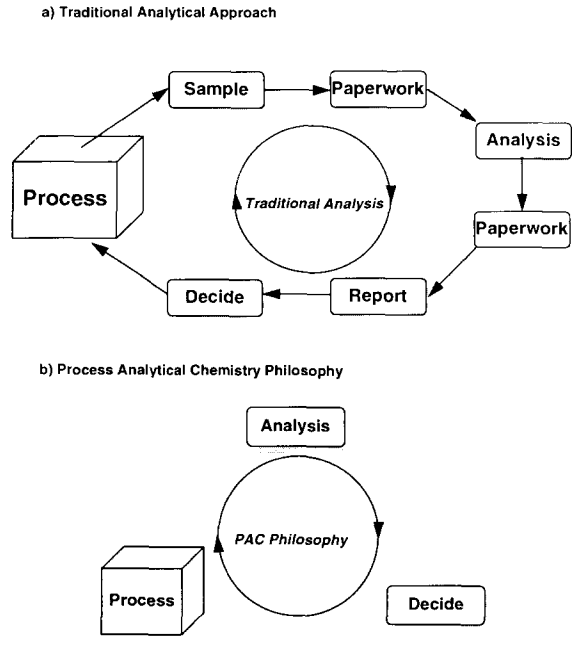

Fig. 1. Traditional analytical approach versus the process analytical chemistry (PAC) philosphy.

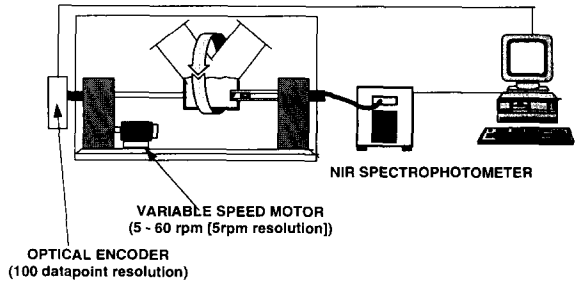

Fig. 2. Schematic diagram of automated on-line system.

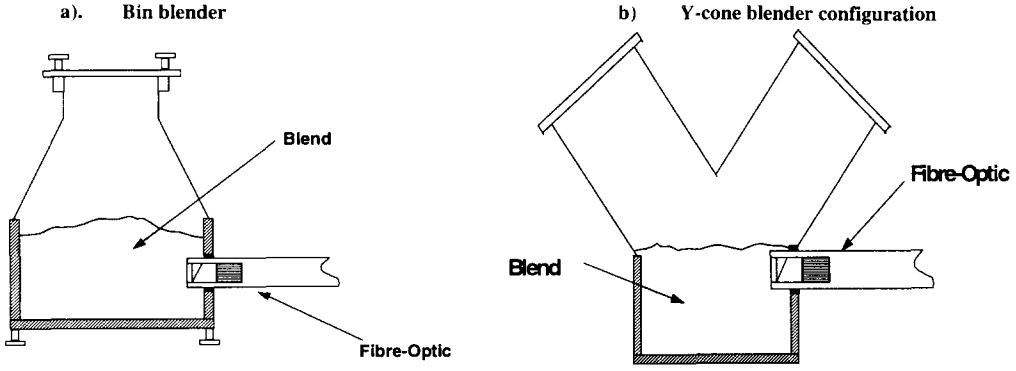

Fig. 3. On-line blender configurations. (a) Bin blender; (b) Y-cone blender configuration.

of 32 scans. All spectra were log ratioed against a reference scan of Spectralon (99% reflective, SRS-99-010, Labsphere, North Sutton, NH, USA). A decrease in the signal-to-noise ratio at longer wavelengths, due to the fibre-optic, require the spectral data to be truncated above 2200 nm.

2.2. Fibre-optic–blender interface

The NIR fibre-optic is interfaced with the blending vessel at the point of rotation. The bearings on the rotational drive unit have been suitably engineered to allow the fibre-optic to remain stationary whilst the blending vessel rotates. The system is shown schematically in Fig. 2. Two blending vessels have been investigated and the coupling of the fibre-optic to the vessels in shown in Fig. 3.

2.3. Software

LabVIEW (National Instruments, Austin, TX, USA) was used to develop the control system software and the graphical user interface. WINSAS (NIRSystems) is a customized software package allowing dynamic data exchange (DDE) of spectral information between the NIRSystems 6500 spectrophotometer and the LabVIEW software.

Table 1
Experimental blend formulation

Component and Source	Concentration (% w/w)
Active (Pfizer Central Research)	10
Lactose (DMV)	45
Maize starch (Roquette)	45

2.4. Hardware

2.4.1. Digital input–output system

The system utilizes an AT-DIO-32F DAQ board (National Instruments). This is a high-speed, 32-bit, parallel digital input–output (DIO) interface for the IBM PC AT and compatibles. The AT-DIO-32F contains three 16-bit counter/timers and double-buffered latches for digital pattern generation and data acquisition. The 32 lines of DIO are arranged into four bytes, which can be programmed by each byte as either an input or an output. The 32 lines may be operated as 8-, 16- or 32-bit ports for handshaking, pattern generation and data acquisition. An AT-DIO-32F equipped PC can serve, as in this case, as a system controller with high-speed DIO capabilities (sampling rate up to 1 MHz).

2.4.2. Shaft encoder

The rotational position of a blender is reported to the DIO board by means of a 100-position Optical Shaft Encoder (RS Components, Corby, Northants., UK) and a custom electronic circuit board. The rotational position is reported as a 7-bit binary number read from the Transitor Transistor Logic (TTL) state of the wires to one of the ports on the AT-DIO-32F board in the control PC.

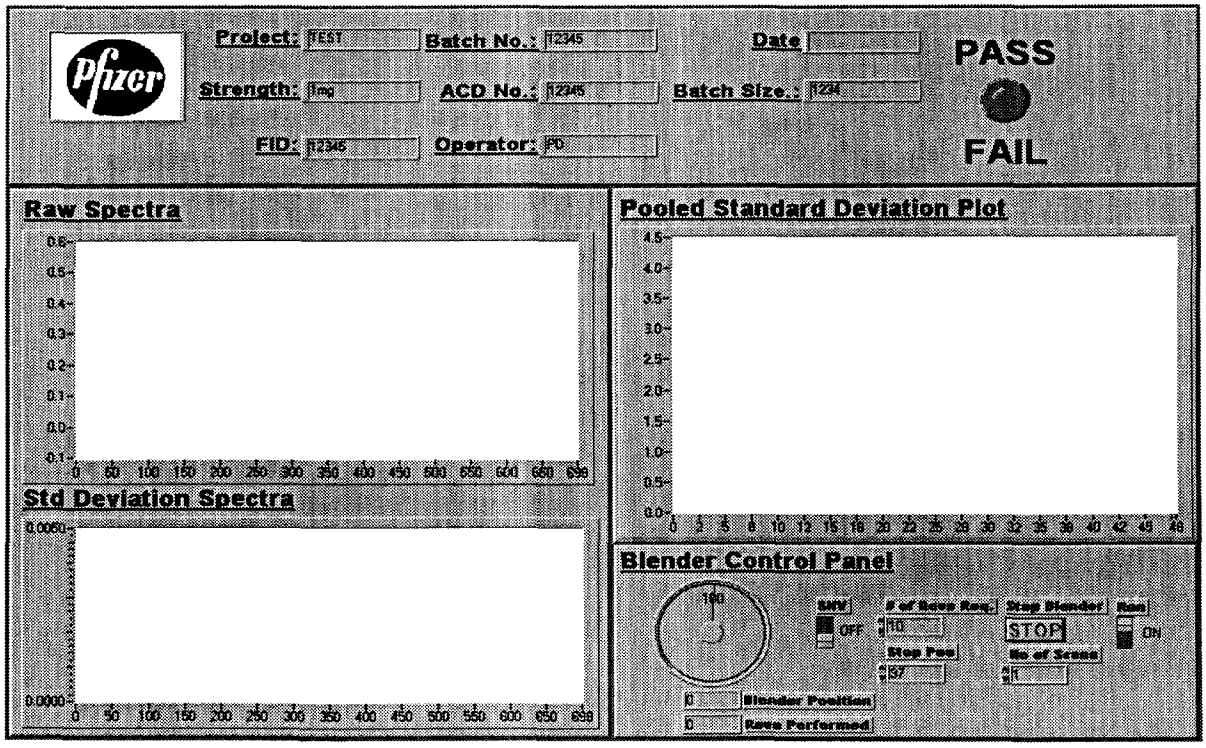

Fig. 4. LabVIEW blender virtual instrument (VI) front panel.

2.4.3. Variable motor control system

The motor control system consists of a FREQROL-U120S-ER general-purpose inverter (Mitsubishi, Hatfield, Herts., UK) controlling the rotational functions of a 0.25 kW variable-speed brake motor (Brook Crompton, Huddersfield, UK). The inverter allows conversion of single- to three-phase power to control the rotational speed of the motor.

2.4.4. HP Vectra XU5/90

The Hewlett-Packard Vectra XU5/90 (Basilica Computing, St. Albans, Herts., UK) utilized in the design of this system is configured with 32Mb of RAM, 1Gb SCSI hard disk drive and has dual 90 MHz Pentium processor capability.

2.5. Experimental blend

To demonstrate the use of the automated blender system, a three-component blend was prepared containing 10% of the active component. Blending was performed in a Y-cone blender for up to 10 min and sampled spectroscopically at 15 s intervals. The formulation composition is detailed in Table 1.

3. Results and discussion

LabVIEW is a software development package designed specifically for instrument control and measurement. The essence of this design concept is based around a programming methodology in which virtual instruments (VIs) are built graphically using icon-based software modules instead of a text-based programming language. In development the VI consists of a front panel interface (Fig. 4) and a block diagram of code that resides behind the front panel (Fig. 5). Fig. 5 also demonstrates the use of sub-VIs within the LabVIEW environment. Sub-VIs perform certain functions that can be assembled and stored as icons for

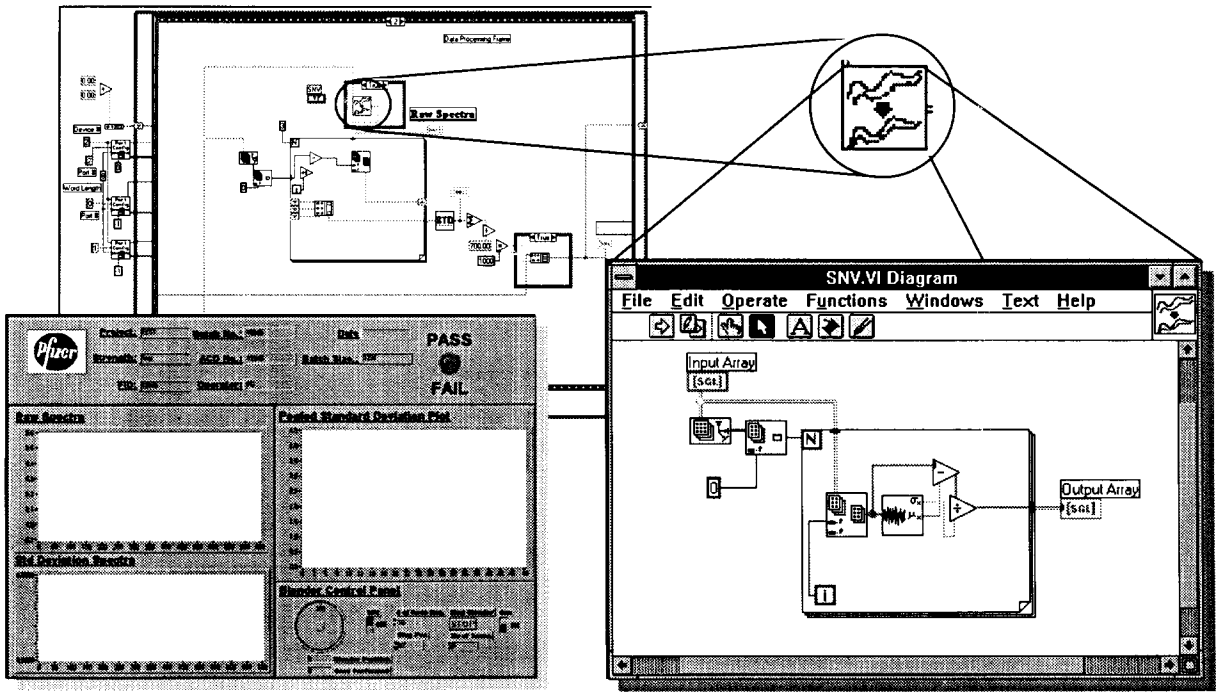

Fig. 5. LabVIEW blender virtual instrument (VI) front panel and block diagram with a typical sub-VI.

future use. In this particular example, the standard normal variate (SNV) calculation is stored as a sub-VI which can be selected from the front panel. The final application built VI consists only of machine code and the visible front panel graphical user interface (GUI) [6]. These GUIs can then be used as standalone executables (*.EXE) operating within WINDOWS but outside the LabVIEW environment. This obviously represents a considerable saving for the implementation of multiple systems.

The sequence structure of the various components of the blender VI is illustrated in Fig. 6. The supervisory control and data analysis (SCADA) software was written in a modular form which can be broken down as follows:

(1) Hardware control and integration (Fig. 6, frame A)
This section of the program reads signals generated by the blender control circuitry from the shaft encoder. The rotational position is read continually from the optical shaft encoder. The custom-built electronic interface device counts the pulses from the encoder, which are then related to a rotational position by utilizing a zero datum pulse from the encoder. Each revolution of the blender is counted and stored in a shift register. The blender is then stopped at a user-defined interval. Additionally, this frame in the sequence structure also instructs the blender to rotate at one of twelve different, pre-set rotational speeds (5–60 rpm) via the FREQROL-U120S-ER inverter.

(2) Software link (Fig. 6, Frame B)
This module performs dynamic data exchange (DDE) transactions with the Spectrometer Control server (WINSAS). Scans are triggered by command from LabVIEW and the raw spectral data is passed back to LabVIEW by DDE for processing.

(3) Analysis module (Fig. 5, Frame c)
This section performs data analysis in 'real time'. In this frame, the LabVIEW software calculates the wavelength standard deviation spectrum, moving average and pooled stan-

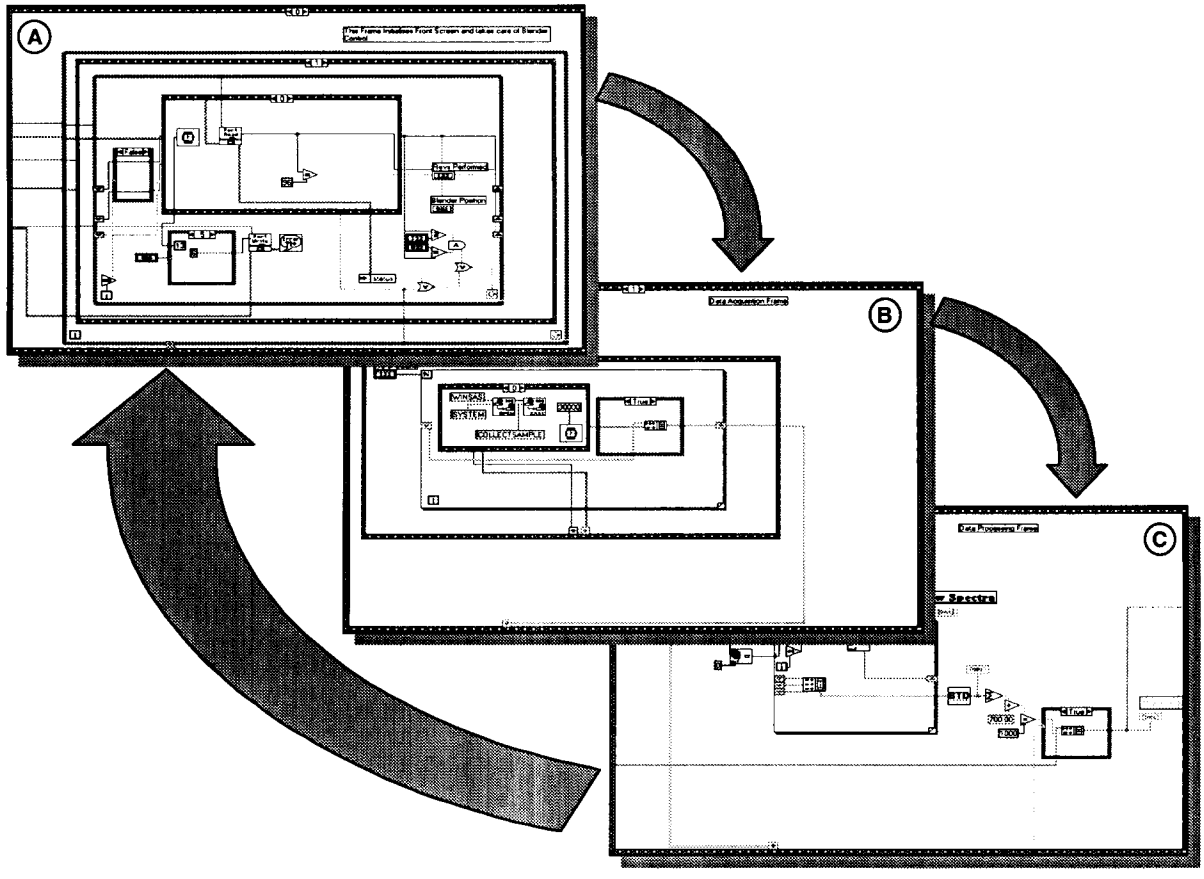

Fig. 6. Sequence structure of blender VI.

dard deviation and graphically outputs the resultant calculation. These will be described later. This frame also contains the Sub-VI for the standard normal variate calculations. Statistical Process Control (SPC) limits are monitored within this module.

The essence of the automated blender system is shown schematically in Fig. 7

3.1. Spectrophotometer control

The NIR spectrophotometer used is based upon the use of a monochromator with a holographic grating. This configuration of spectrophotometer takes around 0.5 s to acquire a single full-wavelength scan and typically requires around 20 spectra to achieve acceptable signal-to-noise values. This results in spectral acquistion times of 10–15 s. The spectrophotometer is therefore not ideal for continuous scanning of dynamic processes such as blending operations as acquiring spectral data over many seconds could result in an incorrect assessment of blend homogeneity. For this reason, the blender was operated in a discrete stop–start fashion with the spectral acquisition being triggered when the blender was stationary.

3.2. Data preprocessing

In diffuse reflectance NIR there is an increase in absorbance at higher wavelengths. This variation is due to scatter phenomena based upon the physical characteristics of the sample resulting in variations in spectral pathlength. In addition, the

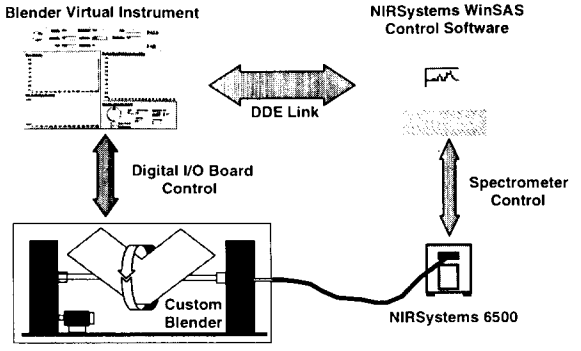

Fig. 7. Schematic of blender control showing hardware and software links.

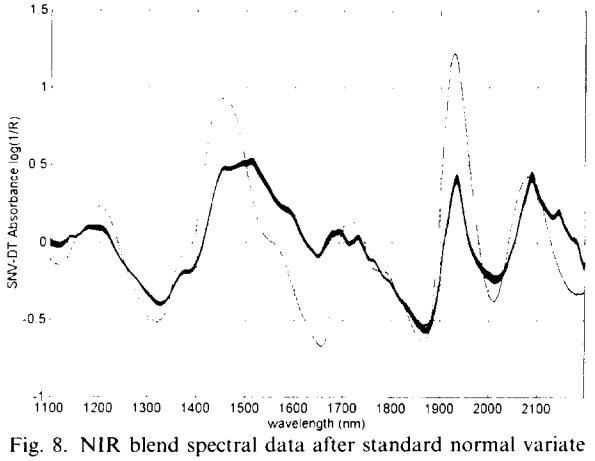

Fig. 8. NIR blend spectral data after standard normal variate (SNV) pre-processing and detrending.

NIR spectra can be curvilinear owing to such parameters as packing density. These phenomena can be removed by a number of pre-processing techniques, but only two approaches will be used here.

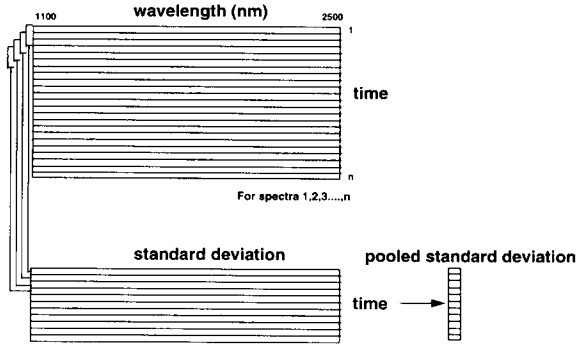

Fig. 9. Moving block standard deviation.

(1) SNV transformation

The SNV transformation [9] removes baseline absorbance shifts and takes the following form:

$$y_{ij} = \frac{x_{ij} - n_i}{S_i}$$

where $i = 1, \ldots, m$ and $j = 1, \ldots, n$ for a data matrix $m \times n$

x_{ij} = NIR spectra

n_i = mean of the elements of x_{ij}

s_i = standard deviation of the elements of x_{ij}

y_{ij} = SNV NIR spectra

(2) Detrending transformation

Detrending fits a second-degree polynomial to each individual spectrum and the detrended spectrum is obtained by subtracting the fitted polynomial from the original spectra.

The combination of SNV and detrend removes the curvlinearity and absorbance offset from the NIR spectra and can reveal important information about the process under investigation. The NIR spectra obtained after SNV and detrending are shown in Fig. 8.

An approach to monitoring powder blending processes is to calculate the standard deviation in both the wavelength and time domains. This approach can begin to reveal information about blend homogeneity and is demonstrated schematically in Fig. 9. The spectral data obtained in real time are analysed using a moving block standard deviation. In this example, the standard deviation of a moving block of three spectra was calculated in the wavelength domain. Pooling the standard deviations for each individual wavelength is a useful diagnostic for monitoring blending processes and is shown in Fig. 10. The moving block standard deviation approach reveals qualitative information about the homogeneity and stability of blending processes and may also be used as a measure of conformance between batches. In this particular example, it can be seen that blend homogeneity is achieved rapidly. There are other chemometric approaches which offer a better insight into total blend homogeneity and combine statistical process control parameters, and these will be the subject of future publications.

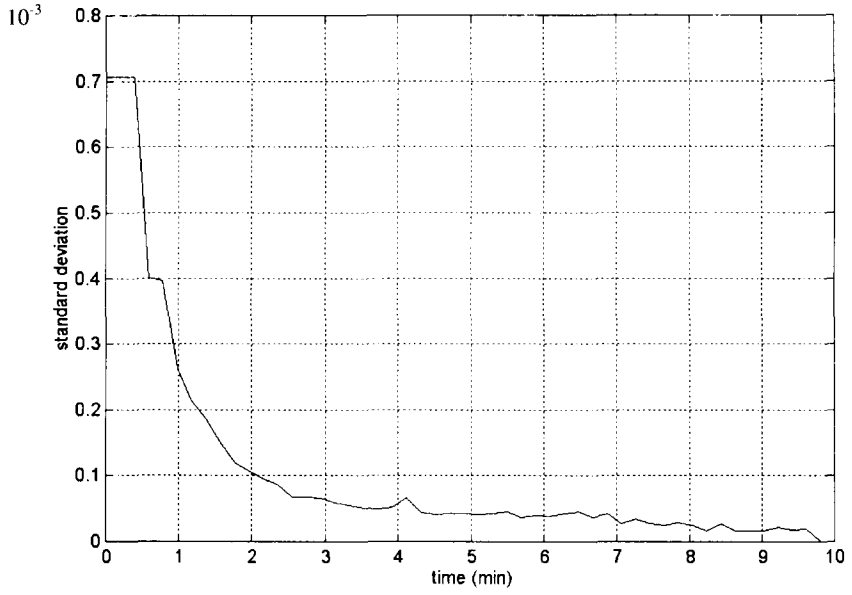

Fig. 10. Standard deviation plot for experimental blend.

The use of the system raises some important philosophical issues. The system will allow sampling of blending processes in real time, revealing information about the active and 'total blend' homogeneity not currently available with the traditional laboratory-based analytical methodologies.

The PAC approach is consistent with the parametric release paradigm which places QA emphasis on the process rather than the final product. For the parametric release of materials, an understanding of the relationship between final product specification and the critical variables during the manufacturing process is required. The ability to monitor blending processes in real time is part of that understanding process and may eventually lead towards the goal of parametric release.

4. Conclusions

It has been demonstrated clearly that NIR spectroscopy can be interfaced with process equipment and, in combination with a fully automated system, can be used for on-line blend analysis. The application of the technology has great potential to meet the demands of clinical and commercial development and manufacture. A reduction in analytical testing requirements and a decrease in manufacturing times would be expected from the use of on-line NIR spectroscopy. PAC approaches to blend analysis do, however, require a number of skills not usually found within the portfolio of a traditional analytical chemist, particularly software, hardware and chemometric expertise. The PAC philosophy emphasizes the need to work in multidisciplinary teams and this can often be the difference between success and failure. The use of software such as LabVIEW for supervisory control and data acquisiton (SCADA) is another crucial parameter in the success of PAC applications as it allows developers to provide application-specific software in a much reduced timeframe. GUIs presented to end-users in the familiar WINDOWS environment is another attractive option. Further publications in this series will discuss alternative chemometric approaches and correlation with HPLC data.

Acknolwedgements

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