AAPS PharmSciTech

AAPS PharmSciTech, 2000; 1 (2) article 10
(http://www.pharmscitech.com)

Next Generation Fluidized Bed Granulator Automation

Submitted: February 22, 2000; Accepted: May 2, 2000

Jukka Rantanen *[a], Markku Känsäkoski [b], Janne Suhonen [b], Jussi Tenhunen [b], Seppo Lehtonen [c], Tarja Rajalahti [d ‡], Jukka-Pekka Mannermaa [a], and Jouko Yliruusi[a]

[a] Pharmaceutical Technology Division, University of Helsinki, Finland
[b] VTT Electronics, Oulu, Finland
[c] Ilmasäätö Oy, Turku, Finland
[d] Whitelake Software Point Oy, Espoo, Finland
[‡] present address, Research Group for Chemometrics, Department of Organic Chemistry, Umeå University, Sweden

ABSTRACT A system for fluidized bed granulator automation with in-line multichannel near infrared (NIR) moisture measurement and a unique air flow rate measurement design was assembled, and the information gained was investigated. The multivariate process data collected was analyzed using principal component analysis (PCA). The test materials (theophylline and microcrystalline cellulose) were granulated and the calibration behavior of the multichannel NIR set-up was evaluated against full Fourier Transform (FT) NIR spectra. Accurate and reliable process air flow rate measurement proved critical in controlling the granulation process. The process data describing the state of the process was projected in two dimensions, and the information from various trend charts was outlined simultaneously. The absorbence of test material at correction wavelengths (NIR region) and the nature of material-water interactions affected the detected in-line NIR water signal. This resulted in different calibration models for the test materials. Development of process analytical methods together with new data visualization algorithms creates new tools for in-process control of the fluidized bed granulation.

KEYWORDS: In-line moisture measurement; Multivariate data analysis; Near infrared (NIR) spectroscopy; Multivariate batch modeling; Principal component analysis (PCA); Process automation

***) Corresponding author:** Jukka Rantanen, Department of Pharmacy, Pharmaceutical Technology Division, P.O.Box 56, 00014 University of Helsinki, Finland; Tel. +358-9-191 59141; Fax +358-9-191 59144; e-mail:jukka.rantanen@helsinki.fi

INTRODUCTION

Demand for automated unit operations in pharmaceutical manufacturing has increased during recent years. Monitoring of critical process steps ensures high quality of the final product. Development of computer capacity and supervisory control and data acquisition (SCADA) systems enables robust and reliable process monitoring and control [1, 2]. Together with novel process analytical applications (e.g., near infrared (NIR) techniques), a new tool for in-process control of pharmaceutics is achieved. On the other hand, automation of pharmaceutical unit operations gives totally new tools for understanding the physicochemical phenomena during processing. A new insight into the process is gained through development of process analytics and data processing methods.

NIR has been widely applied in the field of chemical industry. Use of fiber-optic probes enables noninvasive measuring in the reflectance mode directly from the process stream. Workman et al. [3] reviewed the process analytical applications of NIR. Wet granulation of pharmaceutics was the first process analytical application of NIR in the pharmaceutical field [4-10]. Hailey et al. [11] and Sekulic et al. [12] interfaced NIR spectroscopy with blending process equipment and they used NIR for on-line blend analysis. Monitoring of the film coating process has been reported by Kirsch and Drennen [13, 14]. Hammond et al. used NIR to monitor the progress of the chemical reaction [15].

The present study presents a novel system of fluidized bed granulator automation for research purposes. This study was based on previous automation projects [9, 10, 16, 17]. The air flow rate was measured using flow tube design, and an NIR set-up with a multichannel detector was used for measurement of moisture during granulation. The multichannel NIR set-up accuracy has been evaluated previously [9]. In this study, the

selection of NIR wavelengths is discussed on the basis of full NIR spectra. Principal component analysis (PCA) was applied for the projection of multivariate process data.

MATERIALS AND METHODS

Automation of Fluidized Bed Granulator Description of the System Set-up

The automated system consisted of a hierarchical structure with five levels (**Figure 1**). Readers not interested in the technical details may skip this section.

The supervisory control and data acquisition (SCADA, **Figure 1, level 2**) system was based on FactorySuite 2000 (Wonderware Corporation, Irvine, CA). In the present set-up, InTouch 7.0 (part of FactorySuite 2000) was used as a user interface (**Figure 2**) in a Windows NT 4.0 (Microsoft Corp., Redmond, WA) operating system in a Pentium PC.

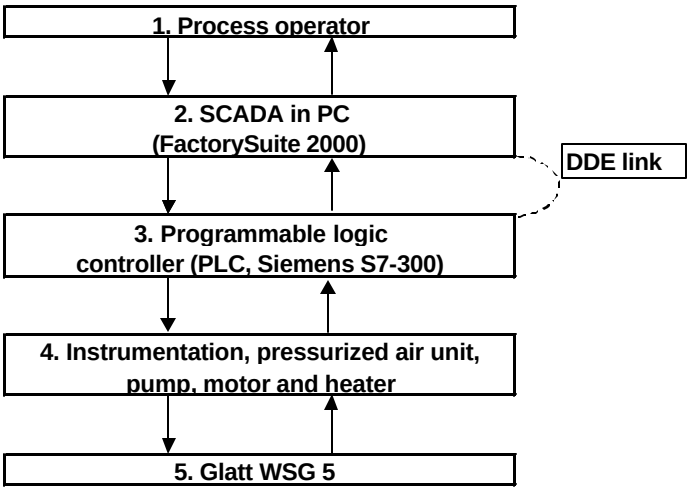


Figure 1. Structure of the automation system.

The programmable logic controller (PLC, **Figure 1, level 3**) unit (Siemens S7-300, Siemens AG, Nürnberg, Germany) consisted of a power supply unit (PS 307), a central processing unit (CPU 314) with 24 kb RAM, a communication module (CP340), and signal modules. The signal modules applied included digital output (SM322), analog input (SM331), and analog output (SM332) modules. The PLC unit programming was performed with Simatic STEP 7 (v. 3.2, Siemens AG, Nürnberg, Germany). The KL3964R DDE Server (Klinkmann Automation, Helsinki, Finland) was used as a DDE (Dynamic Data Exchange) server allowing InTouch to access data on the Siemens S7. DDE is a standard protocol for communication between applications running in Windows environments.

The instrumentation level (**Figure 1, level 4**) included measurement of critical process parameters such as properties of the product, process air and supplied air, granulation liquid, and pressure drops within the process (**Figure 3**).

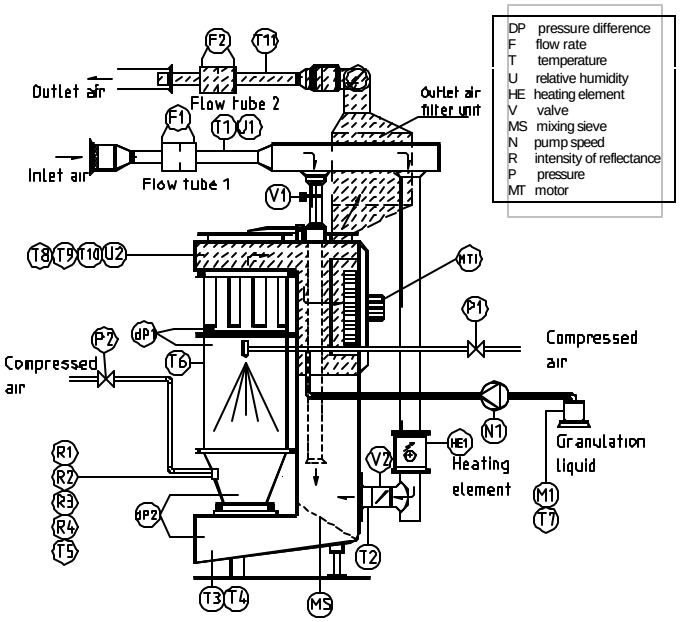


Figure 3. Instrumentation of the fluidized bed granulator.

The instrumentation is described in detail in the following sections. The calibrated ranges and absolute errors of measurements are presented in **Table 1.**

Table 1. Calibrated ranges and absolute errors of measurement.

Measurement	$Range_{min}$	$Range_{max}$	Unit	Abs. error
Temperature	0	120	°C	±0.2 [a]
Relative humidity	0	100	RH%	±3 [a]
Air flow rate	20	160	l/s	±3 [b]
Pressure difference	0	5	kPa	±0.05 [a]
Spraying pressure	0	0.5	MPa	±0.01 [a]
[a] information from manufacturer				
[b] estimation				

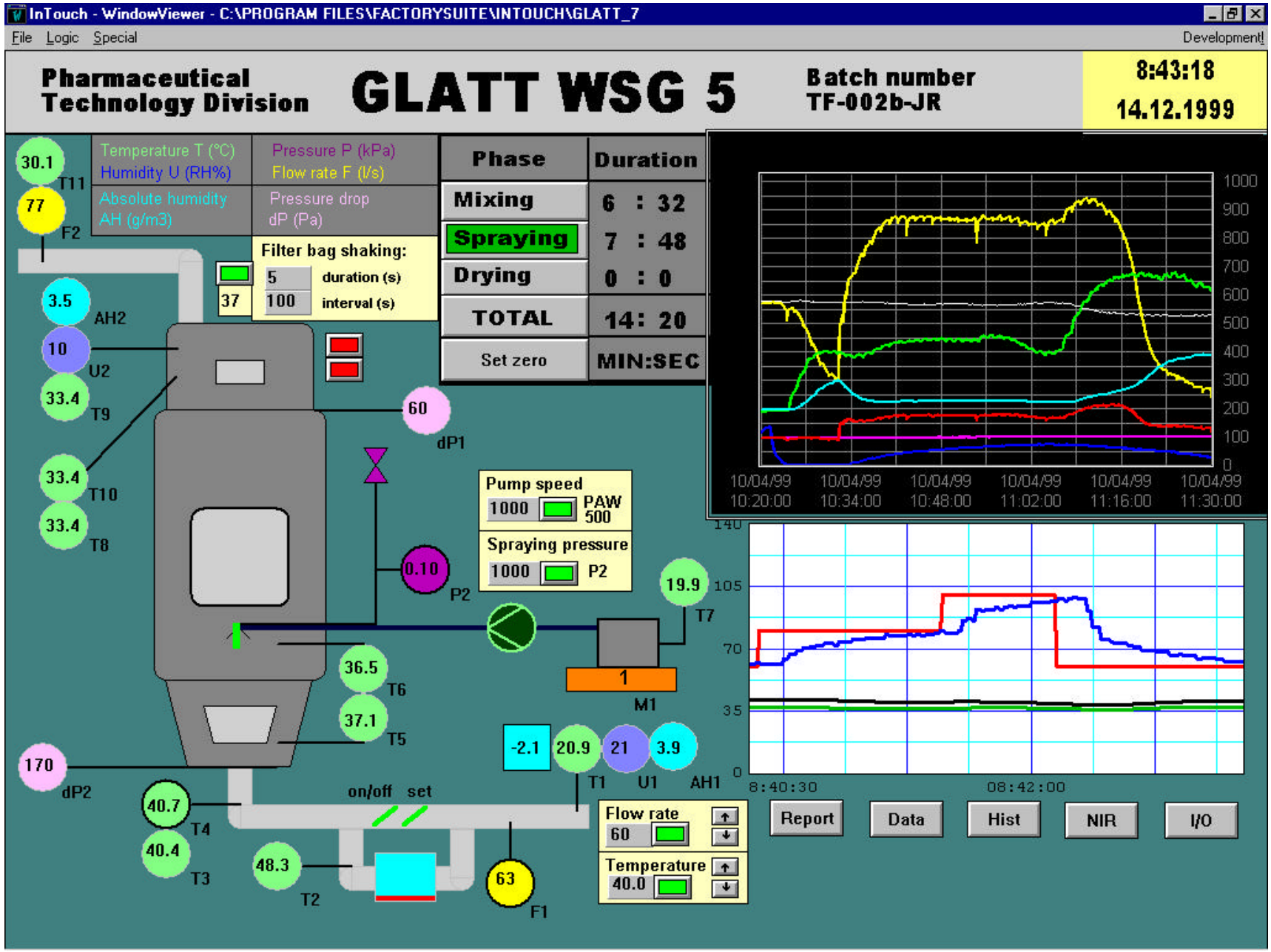


Figure 2. User interface of the fluidized bed granulator.

flow rate of process air was controlled with a frequency transformer (Commander CD, Control Techniques, New Town, UK). The properties of the fluidizing air (flow rate and temperature) were PID (Proportional-Integral-Derivative) controlled.

The pressurized air unit consisted of on-off type regulators (SY5120, SMC Pneumatics, Tokyo, Japan) for controlling the pneumatic devices (e.g., filter bag shaking device). Pressurized air Electro/Pneumatic (E/P) regulators (range 0.005–0.5 MPa, ITV-2030, SMC Pneumatics, Tokyo, Japan) for the pneumatic nozzle and an NIR sight glass were installed in the same housing unit. The pressurized air was filtered (EAF2000, SMC Pneumatics), and the spraying pressure was checked with an accurate pressure measuring instrument (IMT 1875, Industrie Messtechnik, Frankfurt/Main, Germany).

Instrumentation

Process air flow measurement was performed using separate flow tubes (Ilmasäätö Oy, Turku, Finland). The air flow was monitored using flow tube design based on pressure difference over the orifice. A disturbance-free air flow over the orifice was achieved by installing the orifice halfway through the straight tube. The size and the structure of the tubes were optimized off-line in addition to calibrating the pressure transmitters (Micatrone MG-1000-X, AB Micatrone Regulator, Solna, Sweden). The off-line calibration of the air flow measuring system (flow tubes together with pressure transmitters) was performed with valid reference tubes.

Temperature was measured using Pt-100 type sensors (Mikor, Turku, Finland). The housing of sensors was smoothed down in order to achieve a fast response time. All the temperature sensors were calibrated in a water bath.

Relative humidities of the process air were measured using Humicap® capacitive humidity sensors (Vaisala Oyj, Vantaa, Finland) and humidity and temperature transmitters (Humicap 233, Vaisala Oyj). Relative humidity and temperature information were further used for calculation of dew point and absolute humidity of the process air (g H_2O/m^3 dry air). The relative humidity and temperature sensors in these units were checked with a humidity calibrator (HMK15, Vaisala Oyj, Vantaa, Finland).

Process Data Management

The Historical Data Management (Wonderware Corporation, Irvine, CA) provided DDE access to the historical data files created by InTouch. It was used to convert selected historical data into an adequate format, e.g., for MS Excel. All the critical process information during granulation was logged (measurements from the instrumentation shown in **Figure 3**). The DDE link between Matlab (v. 5.3, The MathWorks, Inc., Natick, MA) and InTouch enabled part of the data processing (e.g., filtration of data) to be performed with Matlab.

PCA, a multivariate projection method, was used to reduce the dimensionality of the original multivariate process data matrix. An introduction to multivariate projection methods is given by Wold et al. [18] and Jackson [19]. PCA modeling was performed using SIMCA-P 7.0 software (Umetrics AB, Umeå, Sweden). The mathematical background of the chemometric approach to batch modeling is presented elsewhere [20]. In this study, the process data matrix consisted of twelve critical process measurements at five-second intervals [symbols referring to **Figure 3**: flow rate of process air (F_1), temperature (T_1) and relative humidity (U_1) of inlet air, temperature (T_9) and relative humidity (U_2) of outlet air, temperature of heated inlet air (T_3), granule temperature (T_5), temperature difference between inlet air and granules (T_{diff}), pressure drops within process (dP_1 and dP_2), amount of granulation liquid (M_1), and water absorbence (AWA_1, in-line NIR measurement)].

NIR Measurements

NIR Spectra

Full NIR spectra were measured using an FT-NIR spectrometer (Bühler NIRVIS, Uzwil, Switzerland) with a fiber-optic probe. Diffuse reflectance spectra for solids were measured over the range of 4008–9996 cm^{-1}. Each individual spectrum was an average of four scans and all measurements were performed five times. The spectral treatment was performed with NIRCAL v. 2.0 (Bühler, Uzwil, Switzerland) and Matlab.

The reflectance at 1998 nm was used as a water indicator. The reflectance at 1813 nm was used for baseline correction and the reflectance at 2136 or 2214 nm for normalization. The baseline corrected and

normalized [21] apparent water absorbence (AWA) was determined as follows (Equation 1):

$$AWA = \frac{-\log_{10}\left(\frac{I_x}{I_{x,ref}}\right) + \log_{10}\left(\frac{I_y}{I_{y,ref}}\right)}{-\log_{10}\left(\frac{I_z}{I_{z,ref}}\right) + \log_{10}\left(\frac{I_y}{I_{y,ref}}\right)} \quad (1)$$

where I is intensity (x referring to 1998 nm signal, y to 1813 nm signal, and z to 2214 nm [AWA_1] or 2136 nm [AWA_2] signal) and *ref* is intensity using aluminum plate reference at the corresponding wavelength channel.

Equation 1 was applied for a multichannel NIR set-up, but corresponding AWA values were also calculated from the FT-NIR spectra. Calibration curves were plotted against reference moisture for both the in-line measurement data (AWA from the multichannel set-up) and the off-line data (AWA from the FT-NIR spectra).

Multichannel NIR Set-up

In applications requiring only a few measuring channels, the integrated detector technique [22] has been used instead of the traditional filter-wheel construction. The integrated detector used in this study had four parallel channels, each of them comprising a specific interference filter and a PbS (lead sulfide) detector. The detectors were mounted on a Peltier cooler for stabilizing the temperature below the ambient, and a bead thermistor was used for temperature measurements. All these components were mounted in a hermetically sealed window package.

The NIR sensor in this application was based on reflectance spectroscopy. The optical parts of the NIR sensor were separated into two main modules: the probe and the detection unit. The probe served as an interface between a process and detection unit. It consisted of illuminating fiber and receiving fiber and a sight glass mounted in dust-proof mechanics with heated air purge supplied to the sight glass to prevent contamination. The receiving fiber observed a sample area, which was illuminated by another fiber. The optical signal levels were adjusted by changing the angle of the fibers or changing the measurement distance of the fibers. The detection unit had optics for collecting the optical signal reflected back to the four-channel detector. The detected signal was first amplified in the preamplifier unit. Then the signal was fed to the Phase Sensitive Detection (PSD) unit, where it was filtered with a wide-band filter and recovered with PSD. Parallel optical detection of the multi-wavelength spectrum and parallel PSD-based signal recovery are useful in process monitoring applications. The simultaneous optical detection of the spectrum minimizes errors when, for example, monitoring non-homogeneous material in a continuously moving process stream.

Materials Used in the Granulations

Theophylline anhydrate (BASF, Ludwigshafen, Germany) and silicified microcrystalline cellulose (SMCC) (Prosolv SMCC 50, Penwest Pharmaceuticals Oy, Nastola, Finland) were used as test materials in granulations. In the first phase, the materials (batch size 300 g) were granulated in a planetary mixer (Kenwood KM400, Kenwood Ltd, UK) to where the granulation liquid was added. The granulation liquid used was a 20 w-% polyvinylpyrrolidone (Kollidon K25, BASF, Ludwigshafen, Germany) solution in purified water. FT-NIR spectra of these samples were measured. The same materials were granulated in a fluidized bed granulator (batch size 4000 g for theophylline and 3000 g for SMCC) using the same granulation liquid. Six batches of theophylline (five batches with 3000 g of granulation liquid and one batch with 2500 g of granulation liquid) and two batches of SMCC were granulated. Samples were collected during granulation using a sampling probe (approximately 2 g granules). A reference value for the moisture content of granules was determined using an infrared dryer (Sartorius Thermocontrol YTC01L, Sartorius GmbH, Göttingen, Germany).

RESULTS AND DISCUSSION

Measurement of Air Flow Rate

The air flow measurement was calibrated off-line. The pressure transmitter output from the flow tube was calibrated against the reference method (**Figure 4**).

The nonlinear response was fitted using a second order polynomial (R^2 = 0.9995, $P < .0001$; n = 5). The equation was further used to convert the voltage output into flow rate.

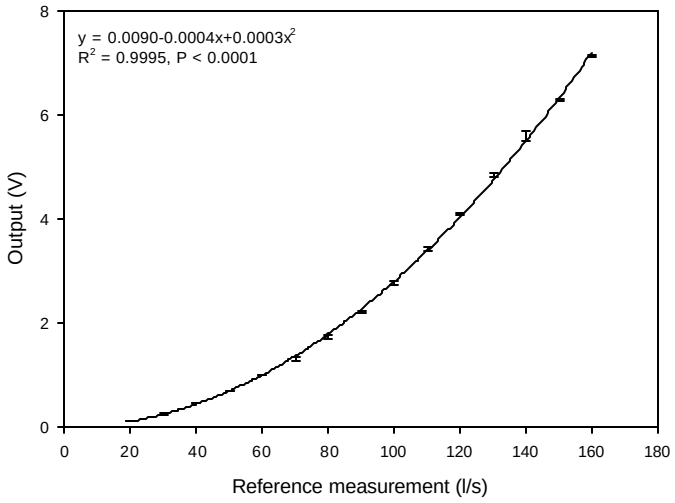


Figure 4. Calibration of pressure transmitter output from flow tube against reference (mean ± SD, *n* = 5).

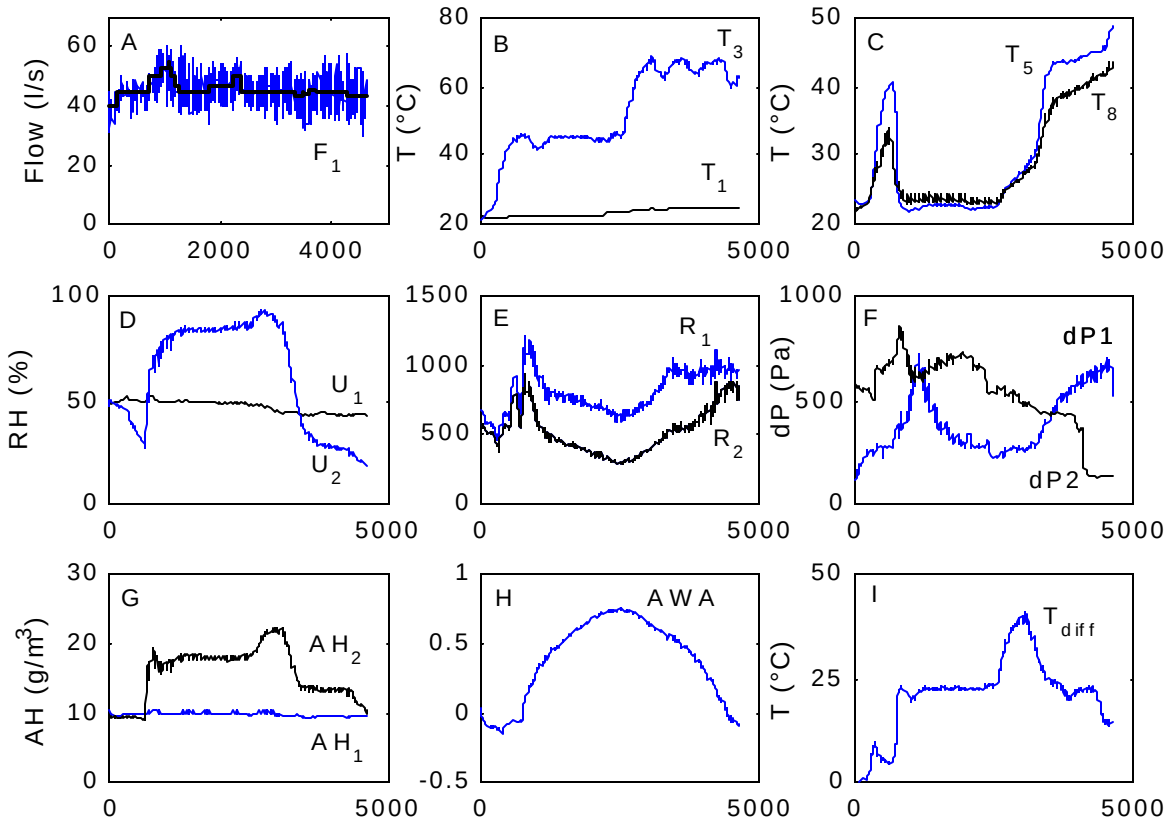
Figure 5. Traditional trend charts from a typical granulation: flow rate of inlet air (A), inlet air temperatures (B), outlet air temperatures (C), relative humidities of inlet and outlet air (D), NIR reflectance signals (E), pressure differences (F), absolute humidity of inlet and outlet air (G), apparent water absorbence (H), and temperature difference between granule and inlet air (I).

Reliable control of process air enables reproducible performance of granulations. Process models based on mass and energy balances may be calculated if the process streams are under control.

Process monitoring

The process trend charts of critical measurements during a typical granulation were plotted (**Figure 5 A-I**, theophylline granulated with 3000 g granulation liquid) using 1-sec intervals. The inlet air temperature set point was 45°C during the mixing and spraying phases and 70°C during the drying phase (**Figure 5B**; T_3).

The typical behavior of granule temperature during different phases of granulation was observed (**Figure 5C**; T_5). During the spraying phase the continuous water film around the granules decreased the granule temperature due to evaporation of water. Water evaporates during this process by the same mechanism as with a wet-bulb thermometer, and the temperature of the solid is near the wet-bulb temperature of the inlet air. Different steps of granule drying were observed as a stepwise increase in granule temperature.



Temperature difference (T_{diff}) between inlet air and granule has been used to detect drying endpoint (**Figure 5I**). Schæfer and Wørts [23] controlled T_{diff} in order to achieve constant drying efficacy of inlet air.

The flow rate of inlet air set point was altered during processing in order to achieve optimum bed performance (**Figure 5A**). The filter bag shaking periods caused interruptions in the flow rate and pressure drop data were observed (**Figure 5A and 5F**).

The reflectance values for 1998 nm signal (R_2) and 1812 nm signal (R_1) decreased in the spraying phase due to the increasing water absorbence and increasing particle size. On the other hand, in the drying phase the reflectance from granules increased due to the decreasing water absorbence and the decreasing particle size. The baseline corrected and normalized AWA can be determined (Eq. 1). The apparent water absorbence (AWA_1) was used for monitoring of water content during processing **(Figure 5H).** Absolute humidity of process outlet air was also used as an indicator of drying endpoint**.** At the end of the drying phase, the absolute humidity of the outlet air **(Figure 5G; AH_2**) reached that of the inlet air **(Figure 5G; AH_1**). Absolute humidity was a more reliable indicator of drying endpoint than the relative humidity of the process air (**Figure 5D**).

Visualization of this highly dimensional data is often difficult. Understanding the state of the process requires granulation experience. For example, the drying endpoint is traditionally based on sampling and knowledge-based decisions made with information from several measurements (T_{diff}, granule temperature, outlet air temperature, absolute humidity, relative humidity, NIR signal, etc.). The dimensionality of the process data was reduced using multivariate batch modeling techniques. PCA and PLS (partial lest squares projection to latent structures) are effective tools for analyzing the process [20]. Björn et al. [24] used PLS for modeling the fluidized bed coating process equipped with an in-line NIR spectrometer. In the present study, the six theophylline batches studied proceeded in a multivariate process space as if through a curved tunnel (**Figure 6**).

The first calculated principal component captures the largest variation in the original data set and the second principal component

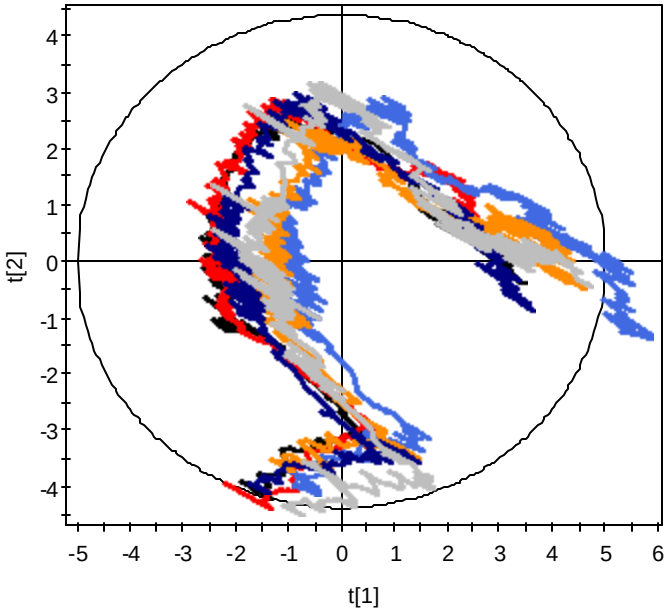


Figure 6. PCA score plot for the six theophylline batches; process trajectories moving through two-dimensional space indicate the state of the process.

improves the approximation as much as possible. These two principal components form a plane in the original process data space (a two-dimensional window into the multidimensional process space). The original observation points can be projected onto this plane. Scores (t) are new coordinates on the calculated plane, and loadings (p) define the direction of the plane. Similar process situations (e.g., different steps of the spraying phase) were projected into the same areas of the score plot. Almost 62% of the variation in the process data matrix was explained by the first two principal components. These two latent variables (summarizing the original twelve in-line variables) described the state of the process in a two-dimensional space (score plot), and the three phases (mixing, spraying, and drying) were clearly visible. Variation in score plot was due to one deviating granulation (theophylline granulation with only 2500 g of granulation liquid) and non-controllable process parameters (inlet air properties). Seasonal effects of process air (variation in relative humidity of inlet process air, U_1) resulted in a deviation in the trajectory as shown in the score plot. These effects could be visualized by creating a PCA model for the drying phase (**Figure 7**).

All drying phases proceeded from the left to the right in the score plot, but there was variation in the direction of

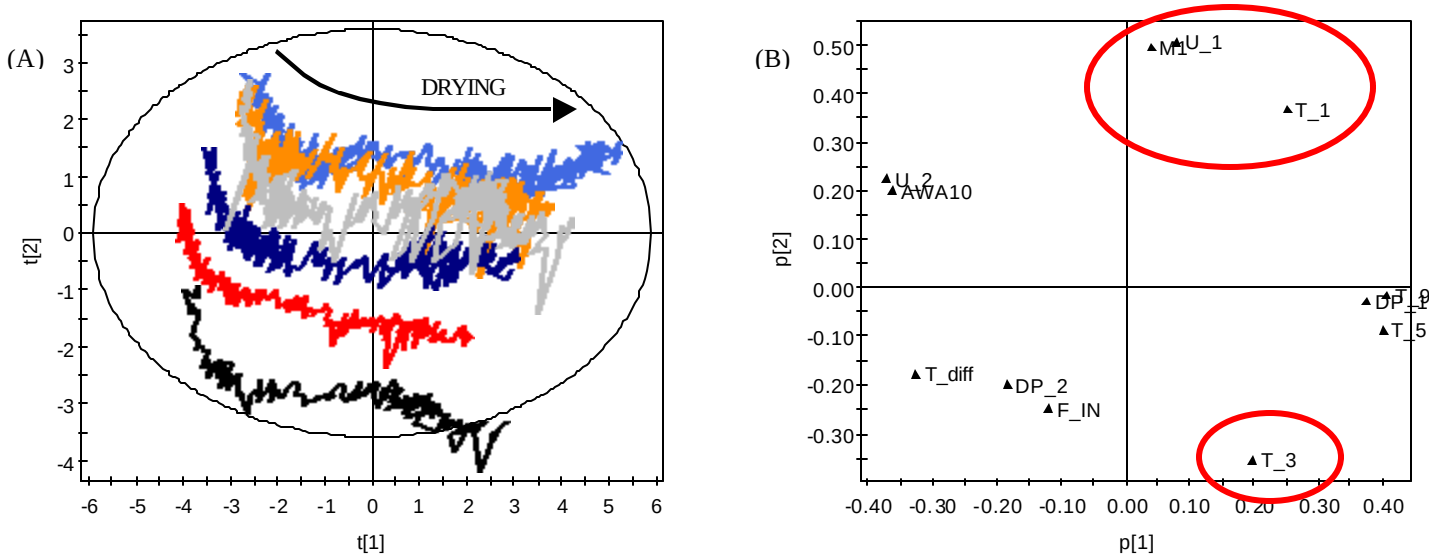


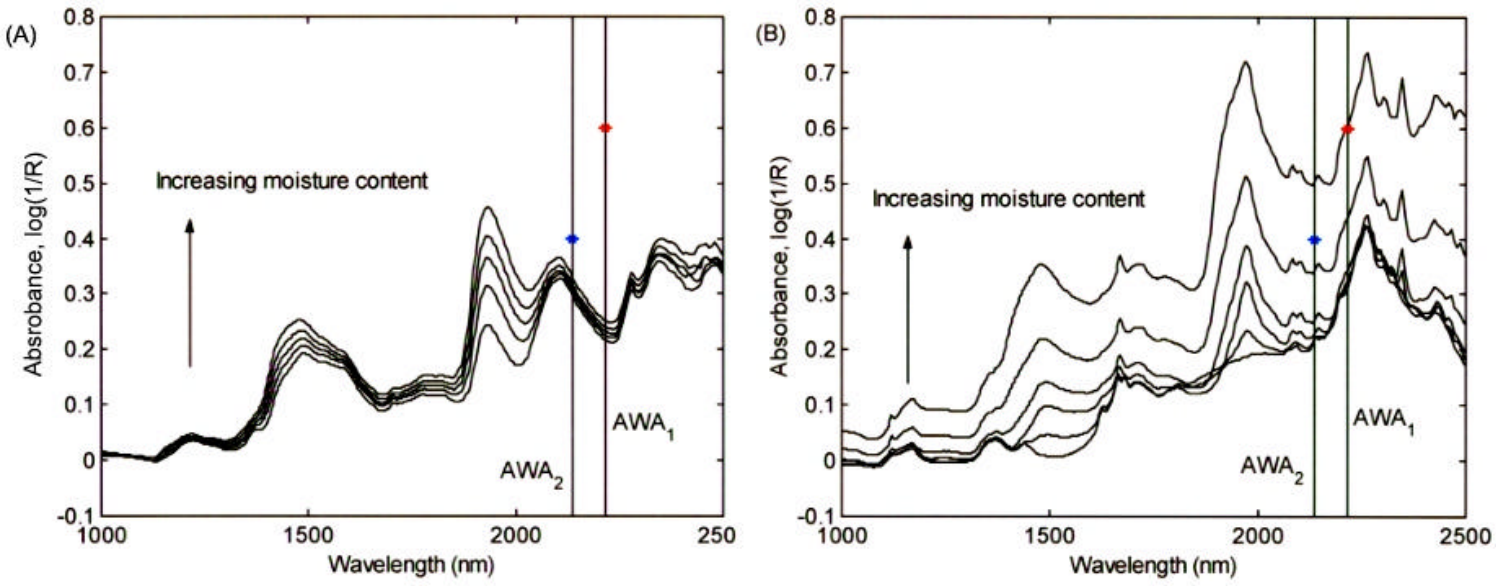
Figure 7. PCA scores (A) and loadings (B) for the drying phases of six theophylline batches.

the second component (t_2 axis). The cause for this behavior can be found in the loading plot; the variables of major importance (resulting in the deviation in the direction of the t_2 axis) are marked with a red ellipse. The amount of granulation liquid (M_1) and inlet air properties (temperatures T_1 and T_3, and relative humidity U_1) were the variables causing the deviation between six granulation drying phases. A set of successful batches (in this case, the four granulations proceeding in about the same way in the score plot) can be used to create the multivariate statistical process control limits describing the normal operating conditions [20].

Spectral phenomena in the NIR region

The FT-NIR spectra of the granulated materials represents the phenomena occurring during granulation (**Figure 8**). Both test materials had water bands around 1450 nm (first overtone of the –OH stretch at 3500 cm^{-1}) and 1940 nm (combination of the –OH stretch at 3500 cm^{-1} with –OH deformation at 1645 cm^{-1}). The reflectance spectrum was affected not only by the increased moisture content but also by the change in the physical state of the sample.

Figure 8. Off-line FT-NIR, log(1/R), of SMCC (A) and theophylline (B) with increasing level of granulation liquid (moisture contents for SMCC 4, 8, 13, 16, and 20 LOD%; for theophylline 1, 3, 6, 11, 16, and 20 LOD%). Vertical lines refer to normalization wavelengths (2214 nm with AWA_1 and 2136 nm with AWA_2).



The nature of the water-solid interactions affects the spectra baseline, which is seen as a rapid upward displacement of log(1/R) spectra baseline with theophylline (**Figure 8B**). In the case of SMCC (**Figure 8A**), the water added was absorbed and the log(1/R) spectra baseline was not displaced as much as that of theophylline. In the present NIR in-line set-up, the changes in spectra baseline were eliminated using the four-wavelength detection around the 1940 nm band.

Further evaluation of FT-NIR spectra showed the nonlinearity of spectral response with theophylline at higher moisture contents (**Figure 9**). The apparent water absorbence values (AWA_1 and AWA_2) calculated from the FT-NIR spectra (**Figure 8**) were linear in the low moisture range, but nonlinearity occurred at moisture contents above 10%. A cubic fitting with theophylline was performed for both AWA values. Theophylline had an absorbence in the 2200–2300 nm region (**Figure 8B**), which resulted in higher AWA_2 values (normalization I_z from the 2136 nm signal) in comparison with AWA_1 (normalization I_z from the 2214 nm signal). The increase in nominator resulted in a decrease in the AWA_1 value. SMCC with absorbence in the 2050–2150 nm region but not in the 2200–2300 nm region (**Figure 8A**) showed higher AWA_1 values than AWA_2 values. Both AWA values with SMCC showed a more linear behavior in the moisture range studied.

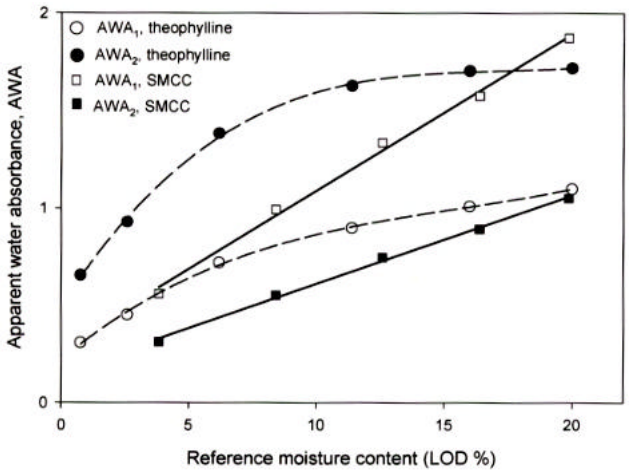


Figure 9. Apparent water absorbence (AWA) values for theophylline and SMCC; calculated from FT-NIR spectra.

Calibration models were also plotted for the in-line samples versus AWA values achieved with the NIR set-up (**Figure 10**).

Again, SMCC showed more linear spectral response. Absorbence around the 2050–2150 nm region resulted in higher AWA_1 values in comparison with AWA_2. Theophylline showed greater nonlinearity, and a cubic fitting was needed as a calibration model. As was observed with theophylline FT-NIR AWA values, the AWA_2 had higher values than AWA_1 due to absorbence around the 2200–2300 nm region. One reason for nonlinearity with theophylline may be the pseudopolymorphic changes during processing. The formation of theophylline monohydrate during wet granulation of anhydrous theophylline has been reported [25].

With both test materials, AWA values from FT-NIR spectra were parallely displaced in comparison with in-line calibration models. This was due to the bandwidth of multichannel detector filters, which was not considered in the calculations. However, the in-line calibration behavior of materials was estimated with off-line samples and FT-NIR spectra.

CONCLUSIONS

Robust process control and measurement system combined with reliable historical data storage can be used for analyzing the fluidized bed granulation process. The application of near infrared reflectance spectroscopy creates a novel tool for direct and real-time measurement of water. Non-direct methods based on temperature measurements do not give exact information on the moisture content of the granules. Further, a critical point in fluidized bed granulation is the measurement and control of process air. Altogether, the measurements performed constitute a measurement vector describing the state of the process. Handling of this multidimensional data requires new tools for data visualization, and PCA modeling proved a promising tool for the reduction of the dimensionality of process data. FT-NIR spectra gave useful information for understanding the phenomena during granulation. The measurement of water content during granulation can be performed accurately with the present multichannel

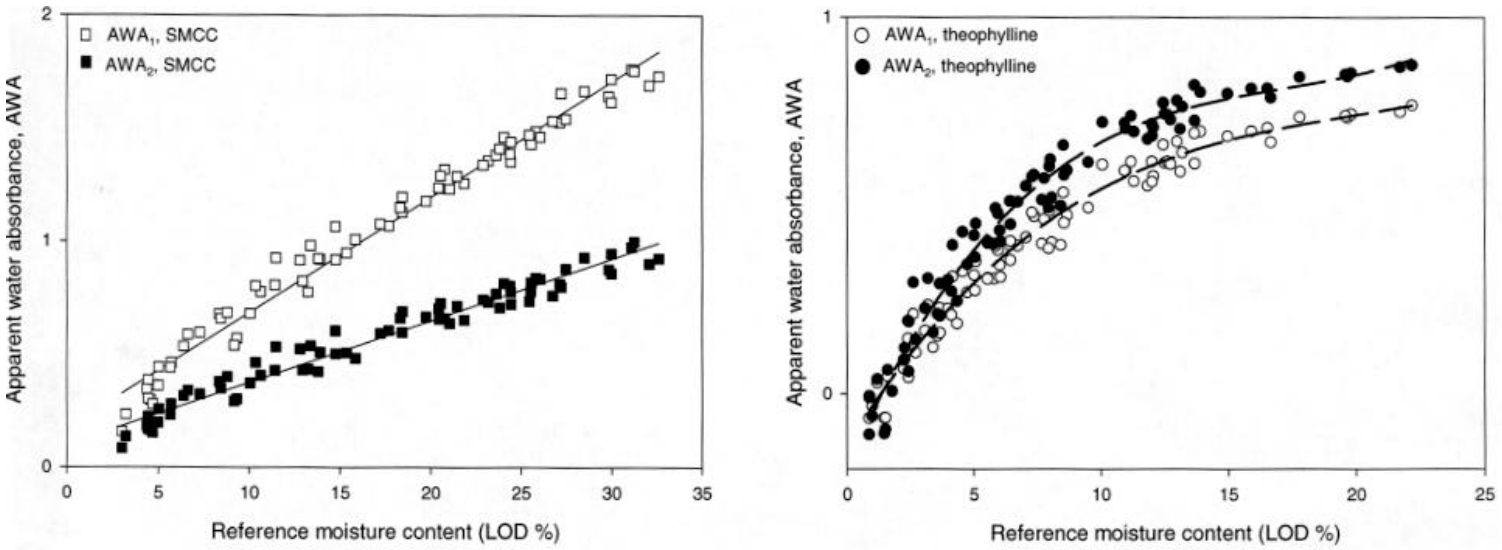


Figure 10. Apparent water absorbence (AWA) values for theophylline and SMCC; calculated from in-line spectral information from multichannel NIR set-up.

NIR set-up. However, the four-wavelength detection proved rather limited for understanding the nature of wetting and drying during the granulation process. Future work should focus on the development of fast and simultaneous detection of several measuring wavelengths. More in-line information could be obtained by connecting various multichannel detector packages into one. Increasing the amount of data collected requires further development of data visualization tools.

ACKNOWLEDGEMENTS

This study was financially supported by the Graduate School in Pharmaceutical Research (Ministry of Education, Finland), Technology Development Centre, TEKES (Finland), and Orion Pharma (Finland). The optical parts used in this study were built by VTT Electronics, Optoelectronics (Oulu, Finland). Pekka Konttinen (Testum Oy, Finland) is acknowledged for the programming of the PLC and user interface. Esko Lauronen is greatly acknowledged for the installation of the instrumentation.

REFERENCES

1. Browne HJ and Olsson KI. Discussion of control systems in pharmaceutical manufacturing. *Pharm Eng.* 1998;18(4):84–92.
2. López O. Qualification of supervisory control and data acquisition (SCADA) systems. *J Valid Technol.* 1999;5(2):148–160.
3. Workman J, Veltkamp DJ, Doherty S, Anderson BB, Creasy, KE, Koch M, Tatera, JF, Robinson AL, Bond L, Burgess LW, Bokerman GN, Ullman AH, Darsey, GP, Mozayeni F, Bamberger JA, and Greenwood MS. Process analytical chemistry. *Anal Chem.* 1999;71:121R–180R.
4. Watano S, Terashita K, and Miyanami K. Development and application of infrared moisture sensor to complex granulation. *Bull Univ Osaka Pref.* 1990;Series A,39:187–197.
5. White JG. On-line moisture detection for a microwave vacuum dryer. *Pharm Res.* 1994;11(5):728–732.
6. List K and Steffens K-J. Überwachung und Steuerung von Granulationsprozessen mit Hilfe der Nah-Infrarot-Spektroskopie. *Pharm Ind.* 1996;58:347–353.
7. Frake, P., Greenhalgh, D., Grierson, S.M., Hempenstall, J.M. and Rudd, D.R., 1997. Process control and end-point determination of a fluid bed granulation by application of near infra-red spectroscopy. Int. J. Pharm. 151, 75-80.
8. Goebel SG and Steffens K-J. Online-messung der Produktfeuchte und Korngröße in der

Wirbelschnicht mit der Nah-Infrarot-Spektroskopie, *Pharm Ind.* 1998;60:889–895.

9. Rantanen J, Lehtola S, Rämet P, Mannermaa J-P, and Yliruusi J. On-line monitoring of moisture content in an instrumented fluidized bed granulator with a multi-channel NIR moisture sensor. *Powd Technol.* 1998;99:163–170.

10. Rantanen J, Antikainen O, Mannermaa J.-P., and Yliruusi J. Use of the near-infrared reflectance method for measurement of moisture content during granulation. *Pharm. Dev. Technol.* 2000; 5: 209-217.

11. Hailey PA, Doherty P, Tapsell P, Oliver T, and Aldridge PK. Automated system for the on-line monitoring of powder blending processes using near-infrared spectroscopy: Part I. System development and control. *J Pharm Biomed Anal.* 1996;14:551–559.

12. Sekulic SS, Ward HW, Brannegan DR, Stanley ED, Evans CL, Sciavolino ST, Hailey PA, and Aldridge PK. On-line monitoring of powder blend homogeneity by near-infrared spectroscopy. *AnalChem.* 1996;68:509–513.

13. Kirsch JD and Drennen JK. Determination of film-coated tablet parameters by near-infrared spectroscopy. *J Pharm Biomed Anal.* 1995;13:1273–1281.

14. Kirsch JD and Drennen JK. Near-infrared spectroscopic monitoring of the film coating process. *Pharm Res.* 1996;13:234–237.

15. Hammond J, Jee RD, and Moffat AC. Monitoring reactions in combinatorial chemistry using near-infrared reflectance spectroscopy. *J Pharm Pharmacol.* 1999;51(Suppl.):22, abstract.

16. Niskanen T, Yliruusi J, Niskanen M, and Kontro O. Granulation of potassium chloride in fluidized bed granulator: Part I. Effect of flow rate. *Acta Pharm Fenn.* 1990; 99:13–22.

17. Merkku P, Yliruusi J, and Hellén L. Testing of an automated laboratory scale fluidized bed granulator using different bed loads. *Acta Pharm Fenn.* 1992;101: 173–180.

18. Wold S, Albano C, Dunn WJ, Edlund U, Esbensen K, Geladi P, Hellberg S, Johansson E, Lindberg W, and Sjöström M. Multivariate data analysis in chemistry. In BR Kowalski (ed.), *Chemometrics: Mathematics and Statistics in Chemistry.* Dordrecht, Holland: D. Reidel, 1984.

19. Jackson JE. *A User's Guide to Principal Components.* New York: John Wiley, 1991.

20. Wold S, Kettaneh N, Fridén H, and Holmberg A. Modelling and diagnostics of batch processes and analogous kinetic experiments. *Chemom Intell Lab Syst.* 1998;44:331–340.

21. Mercer PG. A method of measuring the content of a substance in a film comprising at least one other substance. GB Patent 2 044 443. 1980.

22. Niemelä P. Integrated infrared detectors for industrial process analyzers. *Proc SPIE.* 1988;918:80–84.

23. Schæfer T and Wørts O. Control of fluidized bed granulation: III. Effect of inlet air temperature and liquid flow rate on granule size and size distribution. Control of moisture content of granules in the drying phase. *Arch Pharm Chemi Sci.* 1978;6:1–13.

24. Björn IN, Folestad S, Ström D, Åberg C, and Andersson M. In-line NIR spectrometry — a tool for quality control during fluidized bed coating. 9th International Conference on Near-Infrared Spectroscopy, Verona, Italy, Abstract book O. 5-5. 1999.

25. Herman J, Remon JP, Visavarungroj N, Schwartz JB, and Klinger GH. Formation of theophylline monohydrate during the pelletisation of microcrystalline cellulose-anhydrous theophylline blends. *Int J Pharm.* 1988;151:75–80.