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Cohesive, multicomponent, dense powder flow characterization by NIR

C. Benedetti [a,b], N. Abatzoglou [a,*], J.-S. Simard [b], L. McDermott [c], G. Léonard [a], L. Cartilier [d]

[a] *Université de Sherbrooke, Department of Chemical Engineering, Sherbrooke, Que., Canada J1K 2R1*
[b] *Process Analytical Techniques & Technologies, Product & Process Development, Technology, Wyeth Canada, Montréal, Que., Canada H4R 1J6*
[c] *Axsun Technologies, Inc., 1 Fortune Drive, Billerica, MA 01821, USA*
[d] *Université de Montréal, Faculty of Pharmacy, Montréal, Que., Canada H9W 2M7*

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Abstract

Non-aerated powder flows are frequently encountered in downstream pharmaceutical processes. Such flows occur at the entrance of powder compression units, and their characteristics are of great interest because any powder agglomeration or segregation can be detrimental to the quality of the final solid oral dosage form. This work was aimed at developing a process analytical technology (PAT) method, based on near-infrared spectroscopy (NIR) for the in-line powder flow characterization of pharmaceutical formulations. An Ibuprofen drug formulation was selected for study. A bench-scale hopper system was assembled to monitor powder flow behaviour. An in-line commercial NIR Axsun spectrometer and probe were chosen to collect in-line spectral data on dense, multicomponent, non-aerated powder flow prior to compression. Spectra were collected on flowing mannitol and pharmaceutical product blends. A specially designed, non-contact sampling interface allowed the collection of representative process powder flow spectra without affecting blend uniformity. A partial least squares chemometric model was developed for laboratory-prepared samples, to quantitatively determine the flowing powder's active pharmaceutical ingredient (API) level. Static sample spectra and flowing pure mannitol spectra proved to have a high degree of reproducibility. The model's standard error of calibration was 2.95% of the API level with a R^2 of 0.991. Flowing blend powder spectra and API estimates showed variations consistent with those seen in model samples. The average values for flowing pharmaceutical blends were close to the API concentration, indicating that the proposed procedure was statistically acceptable. The model is considered very promising, and some improvements would lead to its final acceptance at production scale as a PAT tool.

Keywords: Near-infrared spectroscopy; Multivariate data analysis; Content uniformity; Powder flow; Process analytical technology; Powder sampling; Granular systems

1. Introduction

1.1. Context

Pharmaceutical products are currently of high quality, with drug contamination largely being confined to historical accounts of drug regulations (Woodcock, 2005). However, this is due less to improvements in manufacturing processes and more to the adoption of stricter quality control measures as well as regulatory interventions. Such a conclusion is rooted in the relative inefficiency of pharmaceutical manufacturing where production efficiency lies between 2σ and 3σ (Bean and Bruttin, 2002; Carroll, 2006). In contrast, most high-technology industrial production chains (semiconductors, electronics) have efficiencies of 5σ or more. This inefficiency will be problematic in the near future, since it has been established that new formulations of low-dose products will be more common, which may create additional content uniformity and physical stability challenges (Muzzio et al., 2002). These issues are expected to have a high impact on the ability of the pharmaceutical industry to manufacture certain new products (Muzzio et al., 2002).

The principal challenge encountered in solid dosage pharmaceutical manufacturing arises from the complexity of the granular media involved and difficulties in characterizing powder processes. This can be illustrated with thief probes, which are used to withdraw samples in blending processes. It has been shown that these intrusive tools can disturb the powder bed or create segregation during sampling operations, thus potentially rendering the samples non-representative of the process environment (Berman et al., 1996; Muzzio et al., 1997; Venables,

* Corresponding author. Tel.: +1 819 821 7904; fax: +1 819 821 7955.
E-mail address: nicolas.abatzoglou@usherbrooke.ca (N. Abatzoglou).

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2002). Samples are then analyzed outside the manufacturing area by spectroscopic or other methods. While these techniques are labour-intensive, time-consuming, and have severe limitations (Muzzio et al., 1997), they must still be performed to control end-product quality and, in some cases, the critical quality attributes of the processes themselves.

1.2. Powder sampling

The problematics of proper powder sampling, including those encountered with the combination of thief probes and analytical methods, have given rise to several sampling recommendations issued more than 17 years ago. Allen proposed two golden rules for powder sampling (Allen, 1981): (1) powders should only be sampled while in motion; (2) sampling should be done in small increments of time throughout the entire powder stream rather than at the same pre-selected site at all times. More specifically, Staniforth et al. (1989) described the ideal sampling procedure for often-cohesive granular systems seen in pharmaceutical processes. Thus, the ideal sampling technique should:

1. be a simple, reproducible and informative test by which uniformity can be assessed under process conditions;
2. be capable of being performed on powder mixes prior to processing into tablets or capsules;
3. reflect the actual homogeneity of the sampled product likely to be found in the ultimate dosage forms produced;
4. be capable of acting either as a pre-formulation/formulation problem-solving tool, to screen potential formulations at an early stage, or as an in-process quality assurance test prior to compaction or encapsulation (which is now called the quality by design/process analytical technology (QbD/PAT) initiative).

In 2003, the FDA submitted a Draft Guidance addressing the issue of unit sampling and assessment (U.S. Food and Drug Administration, 2003). This Draft Guidance refers to the *use of at-*, *in-*, *or on-line measurement systems.* It was followed one year later by another guidance (U.S. Food and Drug Administration, 2004), which suggested the implementation of PAT solutions to enhance productivity through process understanding and control while maintaining or increasing product quality. The desired state (Hussein, 2005) of pharmaceutical manufacturing and regulation was characterized by the following criteria:

1. Product quality and performance were ensured through the design of effective and efficient manufacturing processes.
2. Product and process specifications were based on a mechanistic understanding of how formulation and process factors affect product performance.
3. Continuous real time quality assurance.

These guidances can be interpreted as a tacit recognition by the FDA that the combination of off-line current sampling techniques (i.e. thief sampling) and analytical methods no longer provide the highest degree of assurance of homogeneous mixtures in pharmaceutical processes and that sampling methods and process understanding must evolve to keep pace as new generations of drugs are developed with lower API (active pharmaceutical ingredient) concentrations. Moreover, processes now require more efficient quality monitoring and control with data management tools to address more rigorous legislation. Thus, several technologies were developed or "rediscovered" for implementation as PAT solutions, such as light-induced fluorescence (Lai et al., 2001; Lai and Cooney, 2004), light reflectance (Gray, 1957; Ashton et al., 1966; Harwood et al., 1971/1972; Weinekötter and Reh, 1994; Gratton-Liimatainen, 1997), effusivity (Roy et al., 2004) and NIR (near-infrared spectroscopy).

1.3. NIR technology

NIR is a fast and non-destructive method that has demonstrated its suitability for industrial and field deployment. Moffat et al. (2000) and Broad et al. (2001) have shown that chemometrics can yield important information on the suitability and applicability of NIR technology in analyzing particulate materials. Indeed, the NIR signal is affected by both the chemical composition and physical characteristics of the sample, including particle size and shape, aeration, porosity, density, humidity and variations in its crystalline structure (European Pharmacopoeia, 2006; United States Pharmacopoeia, 2006). Thus, the use of NIR in the pharmaceutical community has increased in recent years for applications such as product blend monitoring (Popo et al., 2002), film coating monitoring (Andersson et al., 1999), identification of raw materials (Corti et al., 1992), tablet hardness prediction (Kirsch and Drennen, 1999), prediction of active ingredient concentrations (Khan et al., 1997), and prediction of drug dissolution profiles (Freitas et al., 2005). More information on NIR applications can be found in Reich's review (Reich, 2005).

NIR is of interest for drug content determination in finished tablets. Normally, between 10 and 30 tablets, which can be as little as 0.00075% of a batch, are analyzed for drug content. Soto et al. (2005) have shown that on-line NIR could increase the number of tablets monitored by at least three orders of magnitude above standard practice. This would ensure better product quality control and assurance and may help process understanding.

NIR is also of particular interest for blending process monitoring as the flow of granular blends is governed by their physico-chemical properties. The first studies deployed qualitative methods to determine optimal blending time (Cuesta Sánchez et al., 1995; Hailey et al., 1996; Sekulic et al., 1996; Wargo and Drennen, 1996; De Maesschalck et al., 1998; Sekulic et al., 1998; El-Hagrasy et al., 2001; Blanco et al., 2002). Various algorithms were developed to identify this parameter: i.e. moving block of standard deviation, dissimilarity, principal components analysis and others (Sekulic et al., 1998; Blanco et al., 2002). More recently, several researchers were attracted to the possibility of using NIR to quantify mixture compositions. The principal disadvantage was the need for a spectra database on all ingredients in the formulation and their interactions as the

global spectrum of a mixture is not a linear combination of the pure components' spectra (Sekulic et al., 1998).

Therefore, Ren et al. (2000) combined NIR and an artificial neural network with the aim of quantifying an active ingredient (Analgini) in a pharmaceutical mixture of starch, dextrin and magnesium stearate. Duong et al. (2003) studied the homogeneity evolution of magnesium stearate (1%) in a ternary mixture. Samples were collected with a core sampler and were analyzed afterward by NIR. More recently, a similar experiment was performed to investigate the impact of baffles on homogeneity in a Bohle bin blender (Arratia et al., 2006). However, these studies employed off-line measurement techniques to quantify mixture composition. During the manufacturing process, powder is always moving. Thus, there is a need to characterize the effect of sample movements on NIR spectra. Berntsson et al. (2001) found that sample movement (0.046–0.73 m/s) produced features not normally present in the interferograms of an FT (Fourier transform)-NIR apparatus. However, after transformation into frequency domain single-beam spectra, these artifacts did not affect the NIR spectral range. Later, Berntsson et al. (2002) followed the evolution of a binary mixture in a Nauta mixer with in-line FT-NIR.

To the authors' knowledge, the NIR literature on the quantification of flowing powder mixtures is limited to a Nauta mixer case study (Berntsson et al., 2002). Therefore, in this paper, a new NIR non-contact sampling and treatment procedure was developed to allow in-line, real-time characterization of flowing powder mixtures. The procedure was created with the intention of characterizing the homogeneity of flowing powder mixtures during emptying of the hopper prior to the tabletting or encapsulation steps. This is of interest to the pharmaceutical industry as it follows stratified sampling (U.S. Food and Drug Administration, 2003), PAT (U.S. Food and Drug Administration, 2004), and QbD objectives (Woodcock, 2005). Moreover, the procedure is a step forward towards in-process sampling of cohesive blends according to the golden rules of sampling (Allen, 1981). Finally, Staniforth's (Staniforth et al., 1989) recommendations on sampling are respected.

1.4. Scope of this study

The following steps will be reported in this work:

- a scale-down of a direct compression process for pharmaceutical multicomponent formulations of commercial interest;
- a robust, non-invasive, non-destructive and non-contact prototype sampling interface for in-line measurement of flowing powder;
- a sampling technique and protocol to acquire representative samples from the process;
- a predictive PLS (partial least squares) model for flowing API quantification. Results from two series of experiments will be examined: to evaluate the influence of air diffusion on spectrum collection with flowing pure excipient; to quantify API concentration in cohesive, dense, multicomponent pharmaceutical powder flow.

2. Methodology

2.1. Instrumentation

Both series of experiments were conducted in a stainless steel bench-scale tablet press hopper, which was modified for in-line powder measurements by an Axsun NIR system.

An Axsun IntegraSpec XLP 410 NIR analyzer (Billerica, MA) was used to obtain the NIR spectra of mannitol and of a flowing, non-aerated, cohesive, commercial pharmaceutical powder formulation of 13 components. The IntegraSpec XLP 410 was fitted with a 30-mm diameter spot size (13 mm effective measurement diameter) Axsun NIR diffuse reflectance measurement probe (Billerica, MA). The analyzer's specifications are presented in Table 1.

The bench-scale tablet press hopper system (Fig. 1) allowed flow rate control with the butterfly valve and non-contact measurements through the sampling interface. The sampling interface was fitted with a sapphire-glass (Fig. 2).

To have a system similar to the production scale compression unit, the experimental set-up was built in a way to reproduce, as faithfully as possible, the powder flow conditions prevailing upstream of the tablet compression step. Thus, NIR measurements were made under the following conditions:

- the 2-in. outlet diameter was very similar to the outlet used in production;
- a sampling interface was built to enable spectra collection under stable optical conditions;
- all product-vessel contact surfaces upstream of the sampling interface were stainless steel with the same polishing as industrial scale unit surfaces.

Table 1
Axsun IntegraSpec XLP 410 NIR specifications

Equipment	Source	Specification
Axsun OH-CH NIR Analyzer	Axsun Technologies, (Billerica, MA)	Wavelength range: 1350–1800 nm; resolution: 2 nm; number of scans: 20 scans averaged for model-building, 4 scans averaged for run-time; data collect time: approximately 5 s total for model-building, 1 s for run-time (plus a 1 s data-processing phase); serial number: 0052
Sampling probe	Axsun Technologies Optical Bench (Billerica, MA)	Diffuse reflectance projection optics (30 mm/13 effective mm beam) integrated with the flow tube sampling interface for non-contact sampling
Chemometrics and analysis software	The Mathworks (Natick, MA), Eigenvector Research (Wenatchee, WA)	Matlab version 7.04 with PLS Toolbox

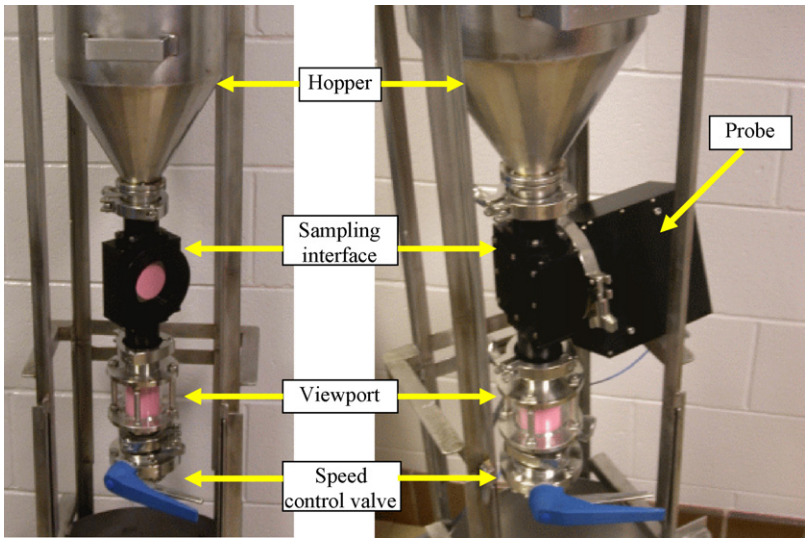

Fig. 1. Experimental set-up.

Differences between the bench-scale set-up and the production-scale tablet press hopper that could affect data validity were:

- the flow rate in the production-scale unit was controlled via a force feeder while the bench-scale set-up was controlled by a butterfly valve which could bring forward an additional segregation potential in our studies;
- the sampling interface in the bench-scale unit was made of Teflon-coated aluminium and possessed a square-shaped cavity that could potentially increase segregation;
- blends for testing were prepared in a small size (1 ft^3) V-Blender with Patterson-Kelly scale-up/scale-down factors for V-Blenders;
- the blends were stored in plastic bags between 24 and 72 h prior to experimental testing;
- the blends were transferred manually from the 1 ft^3 V-Blender to the hopper.

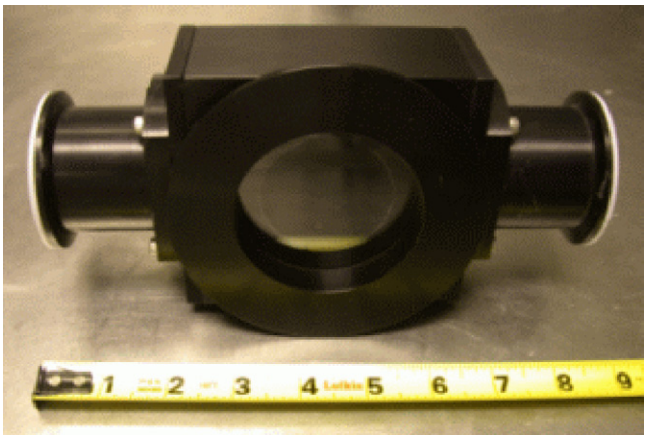

Fig. 2. Sampling interface.

2.2. Raw materials

Three 8-kg mannitol (SPI Pharma, New Castle, DE) batches were prepared for the first experiment. Each batch was used for two consecutive runs. Three 16-kg batches of a 13-component, direct-compression, commercial formulation were prepared for the second experiment. Each batch possessed a different theoretical active ingredient level (75, 100 or 125% w/w of the nominal active ingredient concentration in the commercial formulation) and was split in two 8-kg batches. Each small-scale commercial formulation batch was used for one run and discarded. The active ingredient (API) was ibuprofen (Eurand, Vandalia, OH), representing roughly 15% w/w of the formulation. Mannitol was chosen to balance active ingredient mass change during model building and runs since it was the main excipient and accounted for roughly 70% w/w of the standard formulation. Eleven excipients also were added and blended according to the manufacturing batch record to enhance product colour, compressibility, dissolution, ease of flow and final product parameters.

2.3. Data pretreatment

Spectra were pretreated by standard normal variate (SNV) correction (Barnes et al., 1989) and a Savitsky-Golay first derivative smoothing filter (Savitsky and Golay, 1964), employing 31 data points (3.1 nm) to remove baseline offsets before applying the PLS algorithm.

2.4. Model development

Small-size samples (50 g) were prepared and hand-blended in a bottle with a spatula and rotation of the vial to achieve the desired API concentrations (50, 75, 90, 100, 110, 125 and 150%).

The samples were then transferred on a sampling interface and scanned in static mode. To average a sample's internal variations, it was scanned 10 times while being reblended with a

Table 2
Mannitol experimental plan

Run (#)	Valve opening (notches)
1	3
2	3.5
3	4
4	3
5	3.5
6	4

spatula between scans to average out possible sample nonhomogeneity. No HPLC/UV spectroscopy analysis was performed for API determination since the proportion of each sample was estimated gravimetrically. The room was kept dark to maintain the optical environment as similar as possible to that of the bench-scale hopper.

2.5. Experimental plan

An experimental plan, shown in Table 2, was built to assess whether the Axsun NIR system was appropriate to measure API concentration in multi-component, dense pharmaceutical powder flow. Flow rate was estimated by measuring the time taken to empty the hopper at various valve openings. These average values are reported in Tables 2 and 3. Flow rate uncertainty was the maximum variation observed during replicated runs, independently of the run flow rate.

The first tests were undertaken with pure mannitol, which accounted for approximately 70% of the pharmaceutical blend total mass, to determine whether flow rate and air diffusion had prohibitive effects on spectra collection stability, reproducibility, and to serve as a reference, if needed, for evaluating the impact of flow on the API formulation. The second series of tests, reported in Table 3 with the API formulation, were performed after brief assessment of the granular flow influence on the NIR measurements.

2.6. Experimental procedure

The following experimental protocol was employed for the flowing powder tests:

1. close butterfly valve;
2. load powder into hopper;
3. visually check powder compaction homogeneity through the viewport;
4. allow 5 min for stabilization of the NIR analyser's source. Start NIR data collection. Store static powder spectra in the computer;
5. put a light vacuum near the powder collection bag to ensure negative pressure during powder flow;
6. open the butterfly valve to the desired setting: gravity powder flow start, continue to collect NIR spectra.
7. stop NIR data collection when the hopper is empty.

Table 3
API experimental plan

Run (#)	API (% of the claim)	Nominal mass flow (kg/min)
1	75	1.5 ± 15%
2	75	2.8 ± 15%
3	100	2.0 ± 15%
4	100	2.0 ± 15%
5	125	1.5 ± 15%
6	125	2.8 ± 15%

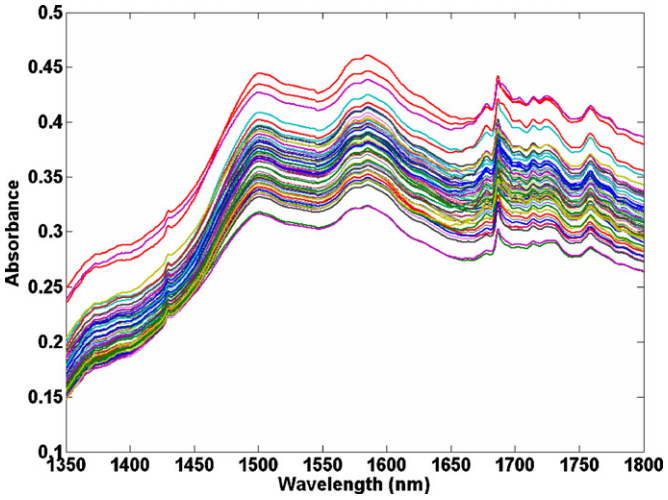

Fig. 3. Raw spectra of samples used for model development.

3. Results

3.1. Model building

Fig. 3 shows all 70 spectra of the small-size samples used for model development. Closer observation revealed large variations in replicated sample scans. This was typical of homogeneity problems encountered when scaling-down industrial formulations, since small-scale equipment cannot replicate exact process conditions. To control this, the 10 spectra of each sample were averaged for model building and pre-treated with both a SNV function and a Savitsky–Golay first derivative, as illustrated in Figs. 4 and 5. The spectral range of 1658–1713 nm was selected for model development, and a PLS model was built with the Matlab PLS toolbox (Eigenvector Research, Wenatchee, WA), using three principal components.

The NIR model was found to be reasonably accurate, as shown by the model-estimated API in Table 4 and Fig. 6. The

Table 4
Theoretical and model-estimated API level

Theoretical API level (%)	Model-estimated API level (%)
50	50.70
75	74.89
90	86.05
100	106.22
110	107.86
125	125.42
150	148.86

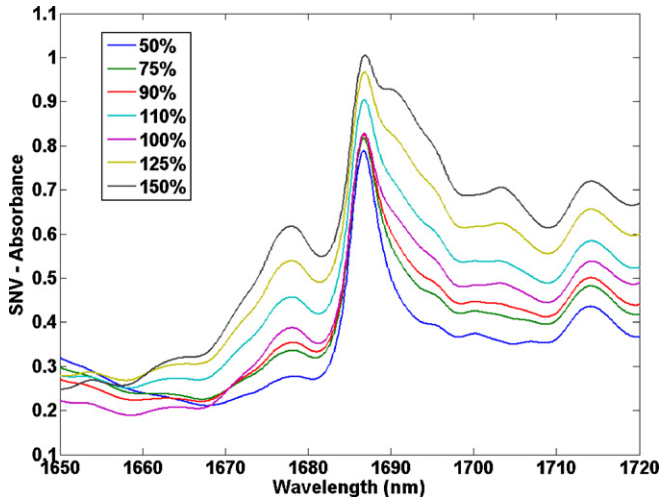

Fig. 4. SNV-corrected average spectra of samples for model development.

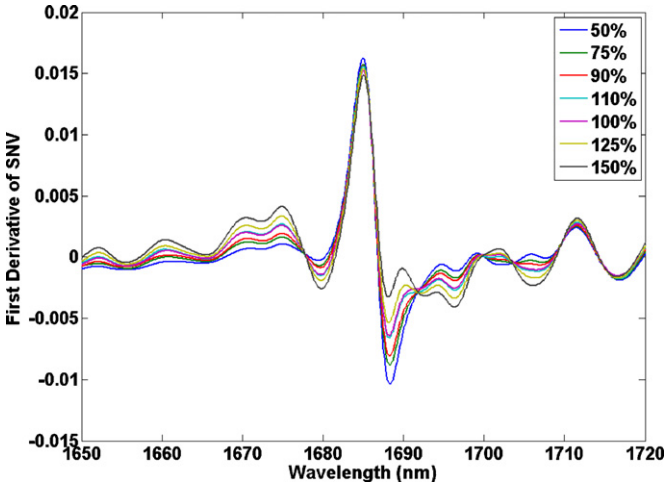

Fig. 5. First derivative of average SNV-corrected spectra for model development.

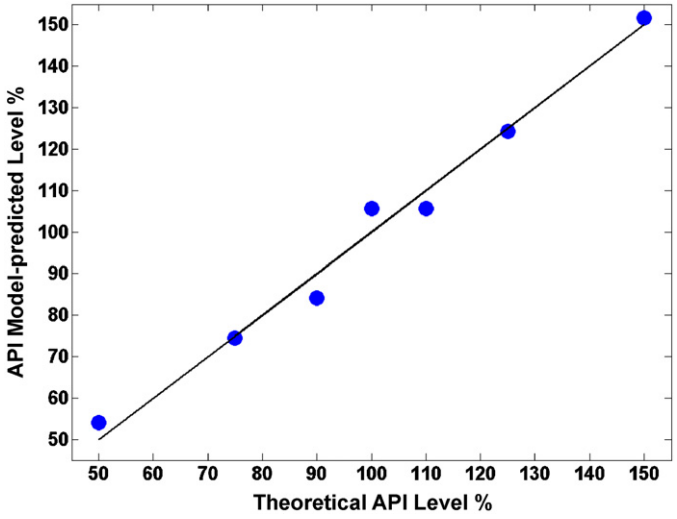

Fig. 6. Fit between targeted API level and model-estimated API level.

model had an R^2 value of 0.991 and a standard error of calibration of 2.95%. An accurate model was anticipated since API mass in the sample is preserved during the process.

Since NIR measures the physical and chemical parameters of samples, it is expected that air diffusion in flowing powder, powder packing density and consequently flow velocity, which, among other factors, affect the above properties, may have an impact on measurement precision and accuracy (European Pharmacopoeia, 2006; United States Pharmacopoeia, 2006). The predictive model built with static powder samples does not account for this influence and may cause additional measurement errors during flowing powder tests. To improve the model, the impact of these factors could be investigated in subsequent studies.

3.2. Flowing mannitol runs

The spectra of six pure mannitol runs were collected. Visual inspections of flow through the viewport showed that, for all flow rates, small random variations were noted but were not quantified. These flow rate variations are included in the macroscopic flow rate measurements. This phenomenon is often observed in cohesive powder flows since the powders do not have the same freedom to relocate as free-flowing powders (Muzzio et al., 2003).

Some mannitol spectra showed slight baseline offsets that may reflect the impact of particle size and particle size distribution, the compaction level (equivalent to bed porosity) and particle flow discontinuity. Data pretreatment removed most of these effects, and the treated spectra were reproducible, as seen in Fig. 7.

The standard deviation of 30 consecutive spectra per run was calculated to effectively compare six flowing mannitol runs of different length. The spectra were selected in the middle of each run to minimize any end effect on the mass flow regime. Standard deviations are summarized in Table 5.

Fig. 8 shows the standard deviation measured for each wavelength during each of the six flowing mannitol runs.

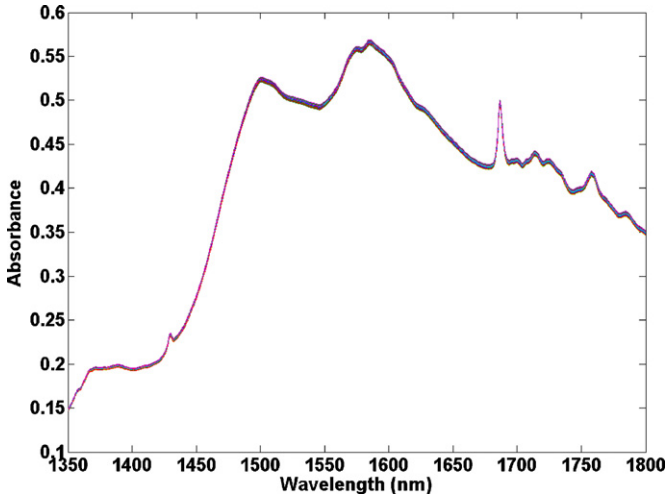

Fig. 7. Flowing mannitol raw spectra (run #1).

Table 5
Flowing mannitol standard deviation

Run	Valve opening (notches)	Average standard deviation
1	3	2.89E−04
2	3.5	2.46E−04
3	4	2.98E−04
4	3	2.84E−04
5	3.5	2.14E−04
6	4	4.79E−04

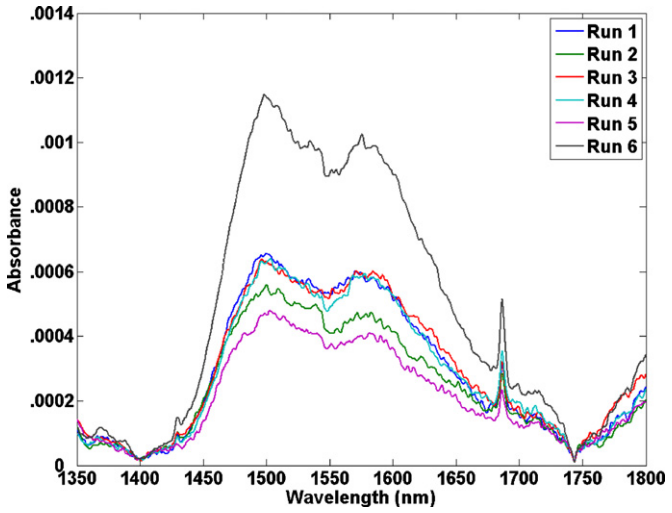

Fig. 8. Flowing mannitol standard deviation.

The standard deviation plot presents very high reproducibility (<1 milli-absorbance unit), indicating good data acquisition and reproducibility. Furthermore, flow rate had a very limited effect on spectral variation, which implied that flowing powder API monitoring was feasible.

Table 6
Flowing blend model-estimated API

	Run 1	Run 2	Run 3	Run 4	Run 5	Run 6
Minimum (%)	54.7	57.6	79.0	83.0	112.0	112.9
Maximum (%)	78.0	83.0	106.9	110.0	138.9	142.8
Model average API (%)	65.9	69.5	92.8	95.4	123.9	127.6
Theoretical API (%)	75	75	100	100	125	125
Standard deviation (%)	5.5	5.1	6	5.8	6.6	5.8
Maximum relative error (%)	18.3	19.4	15.2	15.3	12.1	11.9
Maximum absolute error (%)	12.1	13.5	14.1	14.6	15.1	15.2
Flow rate (kg/min)	1.5	2.8	2.0	2.0	1.5	2.8

3.3. Flowing pharmaceutical lot runs

The spectra of six flowing batches were collected. Visual inspections of flow through the viewport showed the same cohesive behaviour as with the flowing mannitol runs.

Ibuprofen concentration was estimated for flowing batches by a PLS model developed with static samples. The estimated concentrations for all six runs are plotted in Fig. 9 and the statistical characteristics are summarized in Table 6. Sixty consecutive spectra were used for data analysis to effectively compare six runs of different lengths. The spectra were selected in the middle of each run to minimize any "end" effect on the mass flow regime.

Some variability was observed within the readings. This was expected because of spectral variations (due to compositional nonhomogeneity) seen in the constituents during model building and the flow effect. Furthermore, scale-down homogeneity problems were also expected during bench-scale blend preparation. However, the average value estimated during each run was close to the ibuprofen targeted concentration.

Table 6 shows that the model-average predictions were close to the theoretical API values. However, the variations between

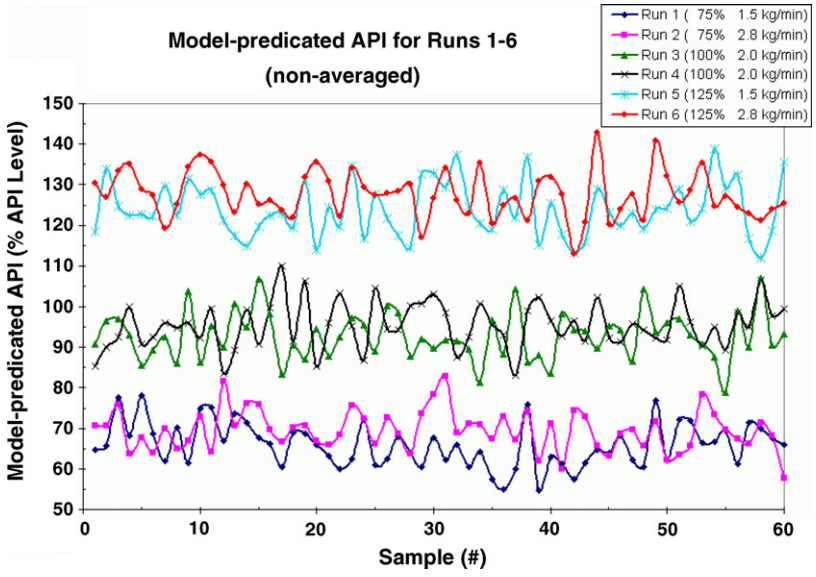

Fig. 9. Flowing blend model-estimated API.

Table 7
API averaging key calculations

	Maximum	Average	Minimum	Units
Flow rate	2.8	2.0	1.5	kg/min
Flow volumetric rate (accounts for density)	4.18	2.99	2.24	l/min
Linear flow speed (accounts for flow section)	0.034	0.024	0.018	m/s
Mass measured in a raw spectra data file	184.2	131.6	98.7	mg
Tablet % measured by raw spectra file	24%	17%	13%	
Averaging required (number of data files)	4.15	5.81	7.75	
Averaging performed for this study (number of data files)[a]	4	6	8	

[a] The number of data files used are calculated by taking the integer of the division of 100% by tablet % measured by the raw spectra file: i.e. 4 = INT (100%/24%); 6 = INT (100%/17%); 8 = INT (100%/13%).

the theoretical and predicted API values were sometimes considered significant by the authors, and model improvement may be necessary before adopting the method on an industrial production scale. Moreover, minimum and maximum measured API values were also within ±20% of the average model prediction for each run.

The maximum relative error for one run was obtained by calculating the maximum difference between the *minimum* or *maximum* value observed and the *model average API* divided by the *model average API* for that run:

$$\text{relative error}\,(\%) = \frac{\text{Max}((\text{ModelAvgAPI} - \text{MinAPI}), (\text{MaxAPI} - \text{ModelAvgAPI}))}{\text{ModelAvgAPI}}. \quad (1)$$

3.4. Averaging of API prediction for one unit dose

Traditional quality control in the pharmaceutical industry imposes the reporting of active ingredient quantity in a sample size varying between one to three unit doses. The following section describes the steps necessary to average NIR API predictions to represent one unit dose of product. This averaging: (a) facilitates data comparison with the above-mentioned norm; (b) renders the NIR technique compatible with Staniforth's third recommendation (Staniforth et al., 1989); and (c) facilitates the application's field deployment in the regulated pharmaceutical industry where reporting analytical results on the basis of "unit doses" is common.

The calculations are based on the following hypotheses:

- uniform NIR powder penetration of 1 mm (recommended by the manufacturer) over a circular probe spot size in the flowing blend as per the manufacturer's specification;
- powder density of 0.65–0.70 g/ml.

Thus, the mass measured in a spectrum of static powder was 88.9 mg, and a unit dose of the studied product was 765 mg. A correction was made to account for flow speed on the mass measured by four spectra at different flow speeds. Key calculations of the API averaging operations are reported in Table 7.

Fig. 10 shows the result of spectra averaging, and Table 8 summarizes the API prediction levels and R.S.D. (relative standard deviation) for one unit dose of product. Model average API levels were identical to non-averaged API levels. This

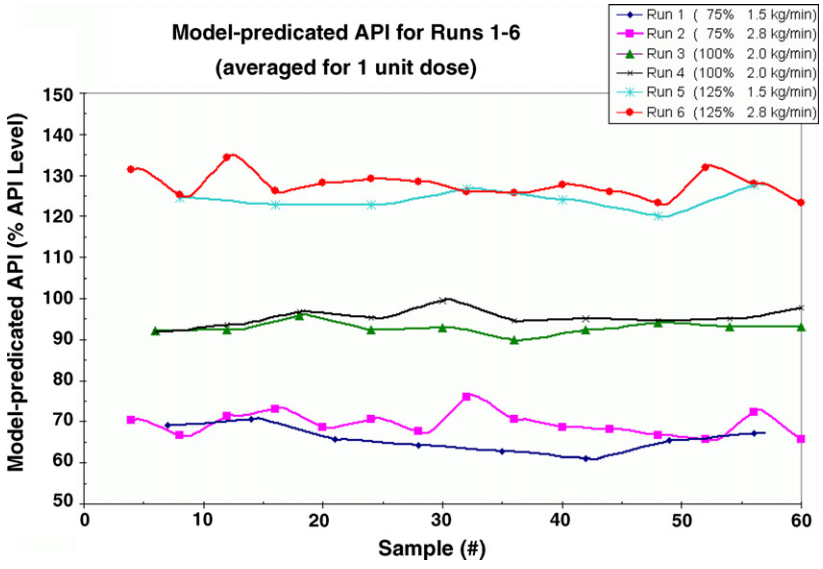

Fig. 10. Flowing blend model-predicted API for one unit dose.

Table 8
Data summary after one unit dose normalization

	Run 1	Run 2	Run 3	Run 4	Run 5	Run 6
Flow rate (kg/min)	1.5	2.8	2.0	2.0	1.5	2.8
Model average API (% API level)	65.7	69.5	92.8	95.4	124.1	127.6
Standard deviation	3.17	2.9	1.49	2.16	2.69	3.09
Relative standard deviation (%)	4.82	4.18	1.60	2.26	2.07	2.43
Number of spectra[a]	56	60	60	60	56	60

[a] "Model average API" and "number of spectra" variation for runs 2 and 5 are caused by averaging: 60 is not dividable by 8. The four spectra excluded from the data set caused small variations of the "model average API".

was expected because the same data sets were used in both cases. The standard deviation and R.S.D. decreased after averaging. This was also expected, considering the larger sample size (99–184 mg) and the absence of trending during the experimental runs.

4. Discussion

We have demonstrated that the NIR technique tested is a simple, in-line, fast, non-destructive, non-invasive, reliable and efficient means of collecting real-time information on flowing, cohesive powder mixtures.

A simple PLS predictive model was developed for quantification of ibuprofen in a 13-component pharmaceutical formulation, using seven powder samples of different ibuprofen levels, spanning from 50 to 150% of the commercial drug's normal concentration. The model's standard error of prediction was 2.9% API with a correlation coefficient R^2 of 0.991.

A bench-scale hopper system was assembled to monitor powder flow behaviour according to PAT principles and sampling theory for application in the pharmaceutical industry. The design allowed in-line NIR spectra collection of flowing mannitol and of a flowing, cohesive pharmaceutical blend (ibuprofen formulation).

Static sample spectra and flowing pure mannitol spectra had a high degree of reproducibility. Flowing blend powder spectra and API estimates showed some variation over short time scales during runs. However, the average estimated API values for flowing ibuprofen were close to the nominal concentrations, indicating that the average measurement was correct, and the observed variations were considerably lessened when they were averaged to represent one unit dose of product. Nonetheless, the observed variations are considered still significant, and optimization is necessary before adopting the method on an industrial production scale in the pharmaceutical industry.

This method for in-line powder monitoring is not restricted to the pharmaceutical industry, and can potentially have different applications. Moreover, considering PAT imperatives, the data collected should allow the pharmaceutical industry to gain process insights and take steps towards Staniforth's goal of full mechanistic information about the behaviour of a given powder system (Staniforth et al., 1989) while approaching *stratified sampling* requirements and the desired state of pharmaceutical manufacturing for the 21st century, as defined by the FDA.

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