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When "homogeneity" is expected—Theory of Sampling in pharmaceutical manufacturing

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A stream sampling method has been developed to facilitate implementation of variographic analysis and use of replication experiments in the development of pharmaceutical formulations. These methods are thoroughly developed in the Theory of Sampling but are not currently used in pharma. Pharmaceutical formulations have very strict requirements as drug products are expected to deliver a specific drug content to patients and are required to avoid possible consequences of over-dosing or under-dosing. Formulation developers currently rely on grab sampling, the use of a sample thief (spear) to extract material from areas suspected of having incomplete mixing ("dead spots"). This study applies an alternative stream sampling approach based on the Theory of Sampling in connection with testing two alternative mixing processes.

The mixing process based on vibration and tumbling can be shown to provide a significantly lower end-point heterogeneity. The results show the usefulness of the variographic approach in combination with replication experiments; both are effective in identifying areas of unacceptable heterogeneity in pharmaceutical blends, and point to the need to continue improving the mixing processes described in this study.

Background

Pharmaceutical manufacturing contains an expectation, indeed a regulatory demand that powder blends that precede tablets and capsules be "homogeneous".

This term is a first collision between Theory of Sampling (TOS) and pharmaceutical industry quality control (QC) practices.[1] Here "homogeneous" does not imply a perfect mixture where the distribution of particles is strictly identical throughout the lot however, but is used to communicate that heterogeneity is sufficiently low that patients will receive a product with the strength "it purports or is represented to possess". These "homogeneous" unit doses are usually required a relative standard deviation (RSD) of less than 5%.[2,3] Quality control units in pharmaceutical manufacturing have a strong interest both in determining the average concentration of a blend, and an equally strong interest in determining how the drug varies throughout a lot (so much for homogeneity in TOS' fashion).

In this study two different methods are evaluated for mixing the active pharmaceutical ingredient (API) and excipients in a pharmaceutical blend. The first mixing procedure involves only tumble mixing. The second procedure involves a vibration mixing step to break the agglomerates of the cohesive acetaminophen particles, and a second tumble blending step.[5,6] Variographic analysis and replication experiments were then used to compare the effectiveness of the two mixing procedures. We show that variographic analysis and TOS could be very valuable in the development of pharmaceutical formulations in combination with near infrared (NIR) spectroscopy. This preliminary work is performed at lab scale but the same approach could be used by personnel at a pharmaceutical company.

Experimental

Materials: The blends were prepared from lactose monohydrate Granulac (Meggle Pharma), microcrystalline cellulose Vivapur 102 (JRS Pharma) and semi-fine acetaminophen (APAP) received from Mallinckrodt Inc. (Raleigh, NC). The lactose monohydrate was passed through a U.S. Standard Sieve 60 (250 µm opening) before mixing.

Calibration Model: An experimental design was followed to minimize correlation between components and obtain a robust NIR calibration model. Three components blends were prepared, (correlation between majority components is unavoidable, and this process reduces the other two), using the experimental design software MODDE 8.0.0.0 Umetrics (Umeå, Sweden). Settings were 14 runs, objective: screening, in a D-optimal design linear model. The concentration range was 50% (relative) above and below the 15.0% w/w (target concentration), resulting in a calibration set spanning 7.5%–22.5% w/w. The experimental design is thoroughly described by Roman et.al.[7]

Preparation of Blends: for the validation of sampling method three blends were prepared, two of 1.5 kg and one of 400 g. The blends consisted of 15% (w/w) acetaminophen (APAP), 66.67% (w/w) microcrystalline cellulose (MCC), and 18.33% (w/w) lactose (LAC). Two mixing procedures were evaluated: 1. mixing in tumble blender for one hour – this was called the T process; 2. 30 minutes of vibration and 90 minutes of tumble blending –- called the VT process. A test set blend (400 g) to challenge the calibration model was prepared with a mixing time of 30 min in each blender.

Description of FT-NIR system and software to develop the calibration model: A Bruker Optics (Billerica, MA) Matrix Fourier Transform (FT)-NIR spectrometer was used to obtain spectra. Calibration and test set spectra were obtained at a spectral resolution of 8 cm^{-1} and a total of 32 scans were averaged. Each spectrum (average of 32 scans) requires about 4.4 seconds. All spectra were obtained as the powder moved at a linear velocity of 10 mm/s, except for the static repeatability test (see below). Under these conditions each spectrum can be estimated to represent approximately 180 mg of powder mixture, based on a depth of penetration of 1.2 mm measured for this spectroscopic system.[7,8] Calibration models were developed in SIMCA 13.0 Umetrics (Umeå, Sweden), partial least squares algorithm (PLS). NIR spectra were pre-treated with a

Table 1. Results of prediction of test set blend (tumble + vibration blender) by the FT-NIR calibration model.

Validation Blend prepared with tumble mixer + vibration mixer, mixed by one hour (T + V)					
Deposition	Average % (w/w) APAP	Std. Dev	RSD (%)	RMSEP	RSEP (%)
n = 1	15.58	0.46	2.93	0.54	4.71
Spectra (#)			68		

standard normal variate transformation and a first derivative based on 17 points. The chemometric model was performed on the 9100 – 5000 cm^{-1} NIR spectral range. The performance of the calibration model was evaluated with independent test blends, aka test set validation.[9–11] Table 1 shows the results obtained in the prediction of an independent test set.

A sampling system was designed to deposit blends over a laboratory conveyor belt for simulating a 1-dim industrial blender outflow sampling/analysis system: Each powder mixture (both calibration – and validation blends) was deposited in a 3 m long, 4 cm wide and 3 cm deep rig by the use of an in-house developed screw feeder.[7] The feeder was operated so as to provide a thick powder bed on the rig. FT-NIR spectra were obtained along the entire 3 m length rig corresponded to approximately 250 g of the 1.5 kg lot powder mixture. The powder surface was left uneven and no attempt was made to obtain a flat surface of powder in the recipient, aiming to produce a highly realistic industrial situation.

Results and Discussion

Real-time analysis of drug concentration was performed by near infrared spectroscopy, as a non-destructive analytical method applied to blender output streams.[8,12] Figure 1 shows the stream sampling system used to obtain the NIR spectra. The drug concentration associated with each spectrum was predicted with the validated PLS calibration model and are shown in Figure 2 for three different blends.[13] The blend marked VT involved both vibration and tumbling mixing as described in the Experimental section, and the blends marked T1 and T2 only included tumble mixing.

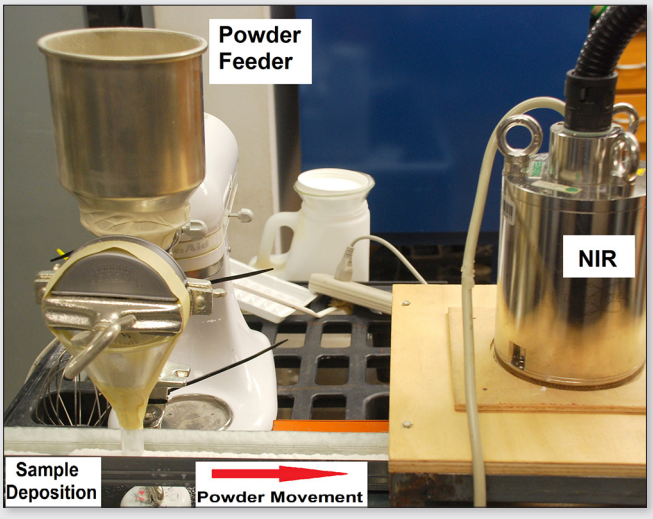

Figure 1. Powder deposition into the 3 meter rig used for moving the powder at 10 mm/sec towards the FT-NIR spectrometer.

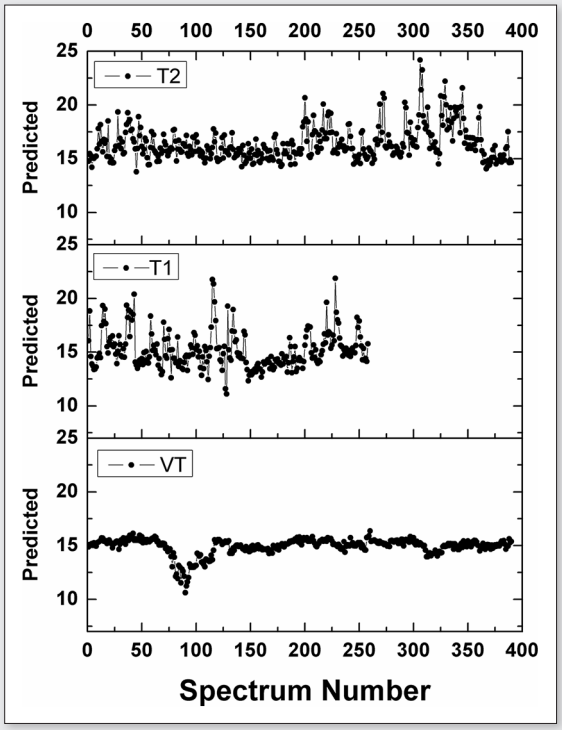

Figure 2. Prediction of drug concentration in three different blends using NIR spectroscopy and the rig shown in Figure 1.

The stream sampling approach also facilitates the use of variographic analysis and the replication experiment[9–11,14], which are virtually new in pharmaceutical blending.[7,8] The Replication Experiment was performed with the three blends (six successive rig depositions, 10 times to-and-fro over just one deposition), and the results are shown in Table 2. Figure 2 shows drug concentration results from a replication experiment where six depositions of 250 g are made onto the 3 m rig shown in Figure 1.

Figure 2 clearly shows that the VT process was superior in mixing to obtain concentrations near the 15.0% (w/w) APAP target level. Particle breaking due to vibration also improved the flow properties of the powder mixture. The central graph (T1) shows less drug concentration results due to difficulties in powder flow and deposition onto the 3 m rig. The VT process showed the lowest standard deviation (0.78% w/w APAP) as shown in Table 2, at least half of those obtained for the T process. The VT process should still be improved due to a drop in concentration observed from spectra #78–116.[7]

Table 2 also shows that the T process has a much higher standard deviation in the replication experiment (n = 10) for a single deposition. The standard deviation of the VT process is 0.34% (w/w) APAP, while the T process blends show standard deviations of 1.06 and 2.02. This replication experiment shows the significant differences in heterogeneity observed. Table 2 also shows similar repeatability study for all blends, since this study is a measurement of instrument (measurement) performance. The repeatability study was conducted by obtaining six consecutive spectra of the same static powder.

The results shown in Figure 2 are important because of the novelty of stream sampling in pharmaceutical blending[15] since most processes have been developed with sample thief ("spear") extracts.[16] Thief sampling has been used to find "dead spots"

Table 2. Comparison of the two mixing methods

	Deposition n = 6 % (w/w) APAP			Replicate of single deposition n = 10 % (w/w) APAP			Repeatability study (n = 6, at 10 points) % (w/w) APAP		
	VT	T1	T2	VT	T1	T2	VT (n = 6)	T1 (n = 10)	T2 (n = 10)
Average	14.93	15.17	16.39	15.21	14.63	16.24	15.78	15.82	15.54
Std.Dev	0.78	1.74	1.58	0.34	1.06	2.02	0.14	0.14	0.17
RSD(%)	5.20	11.46	9.62	2.23	7.25	12.46	1.3	0.88	1.12
Spectra (#)	390	258	390	647	570	650	36	60	60

– areas of incomplete mixing within the blender. The stream sampling approach is effective in showing areas of heterogeneity as shown in this study. The use of NIR spectroscopy to develop pharmaceutical processes is also increasing but most NIR spectroscopic methods are based on a NIR spectrometer installed at a single point (interface) to a blender.[17,18]

Figure 3 shows the variograms obtained for the three processes.[19,20] The three variograms show the very clear differences between the blending processes. The T process shows a significantly higher sill and nugget effect, demonstrating a very high heterogeneity of the outflow material, i.e. the least effective blending. Comparison indicate that the VT process provides a superior mixed-in distribution of the drug in the blend. However, even the best of these tentative processes would not meet pharmaceutical regulatory expectations - yet. A recently withdrawn draft guidance required: 1) a relative standard deviation ≤ 5%, and 2) all individual results within 10.0 percent (relative) of the mean drug concentration.[3] Thus, the stream sampling is clearly effective in finding areas of heterogeneity in the powder blend and simply cannot hide any presence hereof.

The VT process shows a nugget effect - minimum practical error (MPE) of only 0.04% as shown in Figure 3. Thus, the sampling and analysis system is indeed capable of providing a satisfactory very low MPE (the sum of all correct and incorrect sampling errors plus the analytical error, TAE). MPE still depends critically on the heterogeneity of the blend: MPE is greater for the less mixed, more heterogeneous blends.

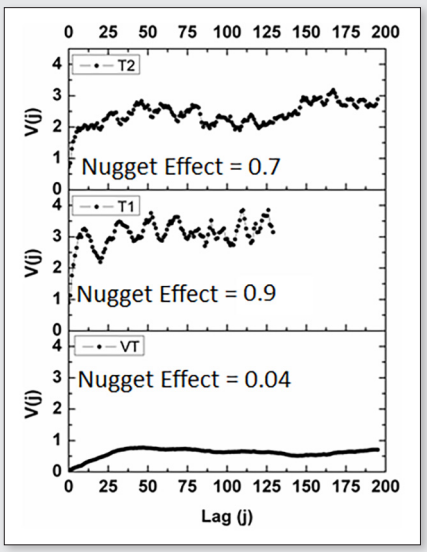

Figure 3. Variograms for the three blending procedures.

Conclusions

The stream sampling method was effective in identifying areas of significant heterogeneity in the powder blends and the need to continue improving both the mixing process, as well as the monitoring approach itself. We regard the present results as very encouraging. This pilot study indicates the way forward for a possible blending process-and-measurement-system development in the laboratory before industrial deployment, i.e. up-scaling, which will always constitute a specific issue to be tackled on a case-by-case basis.

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