Fast in-line NIR in continuous processing for improved understanding of powder mixing and sampling.

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INTRODUCTION

Both in continuous and batch processing of pharmaceutical solid dosage forms, the importance of understanding sampling in NIR-PAT applications for blend uniformity (BU) is well recognized by industry and regulatory bodies. Sampling details such as achieving dose equivalent sample size, sampled fraction and the relation to powder flow and flow geometry are returning issues in development and validation of inline methods. With the recent strong developments in Continuous Processing (CP) of solid dosages, PAT methods for blend or content uniformity in which continuous powder streams are sampled, such as in chute flows[1] or tablet-press feed frame[2], are becoming more prominent and sampling issues more relevant. The present paper describes novel use of high-speed NIR data in CP, yielding, besides chemical information, also information on powder dynamics that is crucial for correct sampling and BU determination in CP (inline with regulatory guidelines)

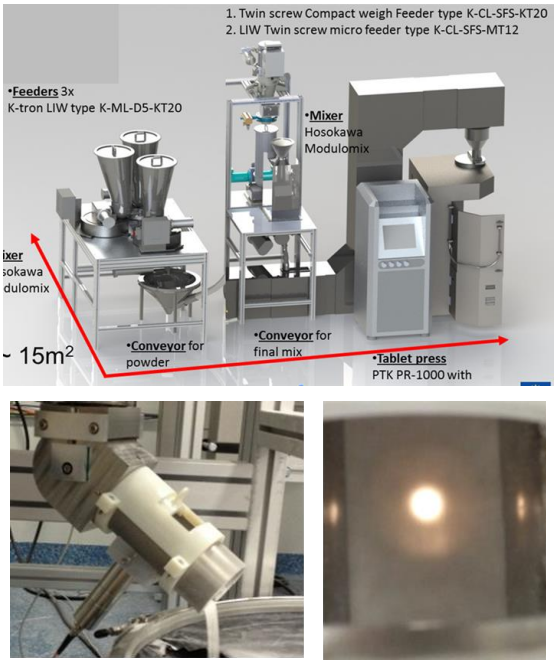

Figure 1. Top: PROMIS line with two mixing stages in the direct compression configuration. Bottom: NIR chute and top view of the NIR spot (3mm diameter) during processing. A 200Hz camera provided powder Imaging velocimetry.

'PROMIS' CP LINE AND METHODS

The versatile 'PROMIS' CP research line (UoEF/VTT), was used in Direct Compression configuration (Figure 1: 3 feeders for API and excipients =>mixer1=>pneumatic transport=>feeders for blend and admixing MgSt +mixer2=>pneumatic transport=> tablet press.) with a ~5% w/w paracetamol formulation. Powder flowing at the outlet of both mixers was sampled using identical chutes with NIR probes (Figure 1) coupled to a 100Hz Multichannel spectral camera. Chemometric models for paracetamol content were built from calibration run data and used to analyze paracetamol content time traces c(t) during processing. Mixing rates were 500-1000rpm at ~5-15 kg/hr.

POWDER DYNAMICS MEASUREMENT BY NIR

Since NIR content predictions should be correlated when subsequent measurements probe overlapping parts of the flowing blend, a new method was devised and tested to infer flow speed from the traces c(t). This is important for powder sampling in pharmaceutical CP since regulatory guidelines require BU data for sample sizes ~ Unit Dose.

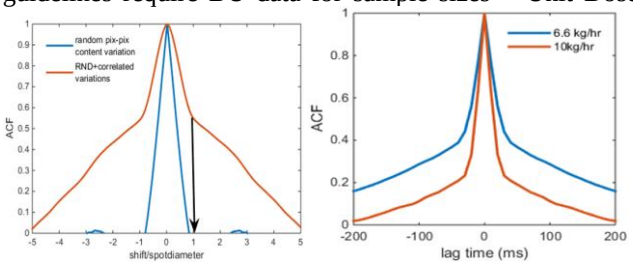

Figure 2. left: ACF's for simulated content traces (see text). Right: ACF's for experimental content traces.

The method uses the autocorrelation $ACF(\tau)=\langle c(t)\, c(t+\tau)\rangle_t$ which should decay rapidly when the lag time τ corresponds to the time that powder on the NIR spot is refreshed. This was tested using simulated data in which (i) API content of subsequent spots is fully uncorrelated or (ii) partly correlated. Resulting ACF's (Figure 2a) show that in both cases the width of the central peak reflects a powder shift corresponding to the spotsize. Experimental data mimic this and using known spot dimension and lag time, flow speed may be inferred from the high speed NIR data.

Resulting flow speeds vs flowrate from the ACF analysis for several process settings reasonably matched the results from imaging velocimetry using a camera (Figure 1).

SAMPLING STRATEGY

Using measured powder speeds and NIR information depth, the number of high speed (10ms) spectra needed to sample a Unit Dose, N_{UD}, can be evaluated. Varying the number of spectra, N_{av}, used to establish the content of each 'sample' has significant effect on BU results, which can be shown by calculating content RSD of samples on the 'scale' N_{av}.

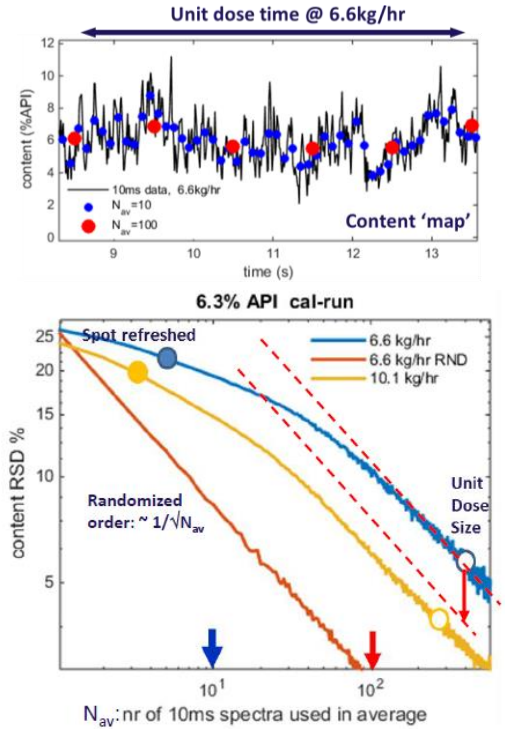

Figure 3. Effective content RSD as function of number of spectra used in the average of each 'sample' (the sampling scale) for time traces at two flowrates (red: randomized time trace).

Results of the analysis are shown in Figure 3 for two flowrates, along with results (red) when the time trace is randomized. The latter show RSD~$1/\sqrt{N_{av}}$ as expected. Actual data show a high RSD when N_{av} corresponds to number of spectra after which the NIR spot is refreshed, $N_{refresh}$. The curved shape for $N > N_{refresh}$ indicates content correlations beyond the spotsize, i.e. blend heterogeneity Importantly, Figure 3 shows that taking arbitrary $N_{av}>N_{refresh}$ to determine the 'sample' spectrum and associated blend RSD, yields incorrect results. Particularly when the blend is not an ideal random 'micro'mix (i.e. heterogeneous, as reflected by the 'curved' log(RSD) vs log(N_{av})), calculating the dose-equivalent RSD from small sample 'size' data ($N_{av}< N_{UD}$) and correcting this using independent sampling statistics (dashed red line ~$1/\sqrt{N}$), can significantly underestimate the actual RSD of the blend on the scale relevant for the product (the Unit Dose).

MIXING/UNIFORMITY EVALUATION PROCESS RUNS

Above analyses were applied to data of mixer 1 and 2 from processing runs at several mixer rpm's and flowrate. The difference between mixer 1 and 2 for a particular rpm/flow is shown in Figure 4. The data for mixer 1 show not only higher overall RSD, but also correlations (curvature in RSD) when $N_{av}<50$ (i.e. 0.5sec averaging). Thus, mixer 1 shows poor 'micromixing'. Since feeder fluctuations within ~0.5sec are negligible and mixer 1, 2 have the same Residence Time Distributions, the data suggests that (lack of) radial 'micro'mixing (not accounted for in standard RTD models for $RSD_{out}=f(RSD_{in})$) plays a role. Data for mixer 2 show negligible heterogeneity beyond the spot size ($N>N_{refresh}$), i.e. improved mixing on scales < the Unit dose.

Final BU results in terms of Unit Dose equivalent RSD's were analyzed for all runs and showed an RSD reduction of a factor 2 between mixer 1 (RSD~5%) and mixer 2 (RSD~2.5%), with little dependence of RSD on process settings in both cases. The final RSD is close to the intrinsic RSD for this formulation calculated from the API Particle SizeDistribution, showing that the two stage CP can adequately process a relatively low dose formulation.

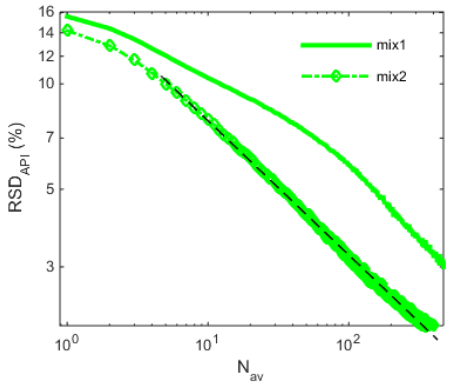

Figure 4. Effective content RSD versus N_{av} for content traces of mixer 1 and 2, at identical rpm, flowrate (same flow velocity).

CONCLUSION

A method is presented to estimate powder velocity from the dynamic NIR spectra during CP. Results show that high speed NIR spectroscopy with appropriate correlation analysis yields, besides traditional chemical info, also information on powder dynamics relevant to sampling. Without knowledge of flow speed, or using inappropriate sampling rate, blend RSD's (at 'dose-equivalent' sample size) can be significantly over/underestimated. The developed methodology for assessing powder dynamics and sampling approach therefore contributes strongly to validation of NIR-PAT methods for Continuous Processing.

REFERENCES

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2. Mateo-Ortiz, D.; Colon, Y.; Romanach, R.J.; Méndez, R.; J Pharm. Biomedical Analysis 100 (2014) 40