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Moisture Endpoint Detection and Scale Up for Top Spray Granulation Technology

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PURPOSE

Top spray fluid bed granulation is a common method of wet granulation involving one or more wetting and drying cycles. Moisture content during the wetting cycle is one of the most critical factors that influence agglomeration rates and overall particle growth. Measuring moisture content during processing normally requires removing a small sample from the fluid bed and placing on a loss on drying (LOD) system to evaporate the moisture and determine the weight loss percentage. These machines typically take between five to fifteen minutes, during which time it is likely that the moisture content has changed significantly from when the sample was pulled. This could be detrimental to the process if the material is on the verge of being oversaturated and end up crashing the batch. Using NIR spectroscopy, it is possible to create a correlation between absorbance and product moisture, which provides instantaneous feedback on moisture content and greatly decreases the likelihood of over-wetting and crashing the entire batch. It can also be used to predict when the material is finished drying, leading to potentially shorter drying times if an LOD system is not needed and material can be discharged after reaching the target absorbance value. The goal of this study was to produce repeatable moisture curves for a placebo product and an APAP product that can predict endpoint moisture for both wetting and drying steps and be able to scale that from a lab scale unit up to production using the same moisture curve.

METHOD(S)

Top spray granulation trials were conducted using the VFC-15M FLO-COATER® (Freund-Vector Corporation) with a 20L container and the VFC-60M FLO-COATER® (Freund-Vector Corporation) with a 220L container. The NIR filter photometer (ITG) was used for measuring in line moisture content, while the Mark-3 moisture analyzer (Sartorius) was used for offline moisture measurements. For both units, a placebo formulation consisting of 70% lactose (Lactose 312) and 30% microcrystalline cellulose (Emcocel 50M) along with an active formulation of APAP (Semi fine). The placebo blend was granulated using a 10% PVP K30 solution to a theoretical 5% w/w weight gain. The APAP was granulated using the same solution but went to a final theoretical 7% w/w weight gain. The process was considered finished when the final moisture content was below 2%. Batch size for the placebo blend was 4kg in the 20L container and 75kg in the 220L container. For the APAP blend, batch sizes were 3kg in the 20L container and 60kg in the 220L container. Hausner ratio, Carr's index and angle of repose were all measured to determine flowability properties and particle size distributions were measured using the QICPIC Particle Size Analyzer (Sympatec).

RESULT(S)

Placebo granulations were done using a 70% lactose 312 monohydrate and 30% microcrystalline cellulose 50M and 5% PVP K30 binder addition via the spray system. APAP granulations were done using 100% semi fine APAP and 7% PVP K30 binder added via the spray system. After running calibration batches, the moisture content measured by the NIR filter photometer averaged over 30 seconds was within 1% of the confirmed moisture content measured by the Mark-3 moisture analyzer at each interval that a sample was taken. Graphical representation is shown in figure 1. Physical characteristics of each batch matched closely when similar moisture profiles were used during the granulation process as shown in the table 1. Assuming a Hausner ratio lower than 1.34 is considered passable, all the granulated products fall into that range while the raw materials are over 1.4 which is in the poor to very poor range. Carr's index also confirms that the granulated materials are passable or better, while the raw materials are poor or worse. Angle of repose was also measured for the granulated products, but since the raw materials did not flow well enough for a measurement, no comparison can be made between the starting and ending material using this metric.

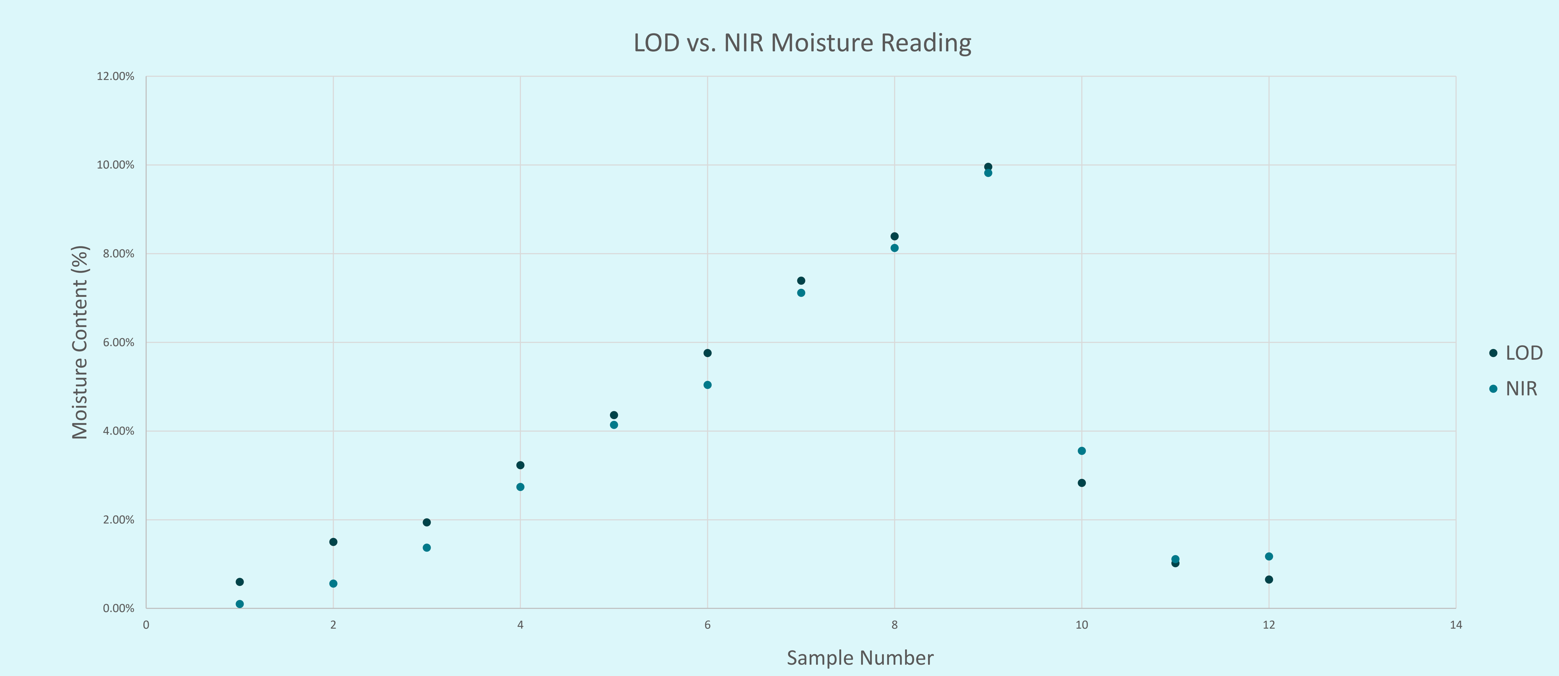


Figure 1: NIR moisture output vs. Sartorius Mark-3 moisture analyzer reading

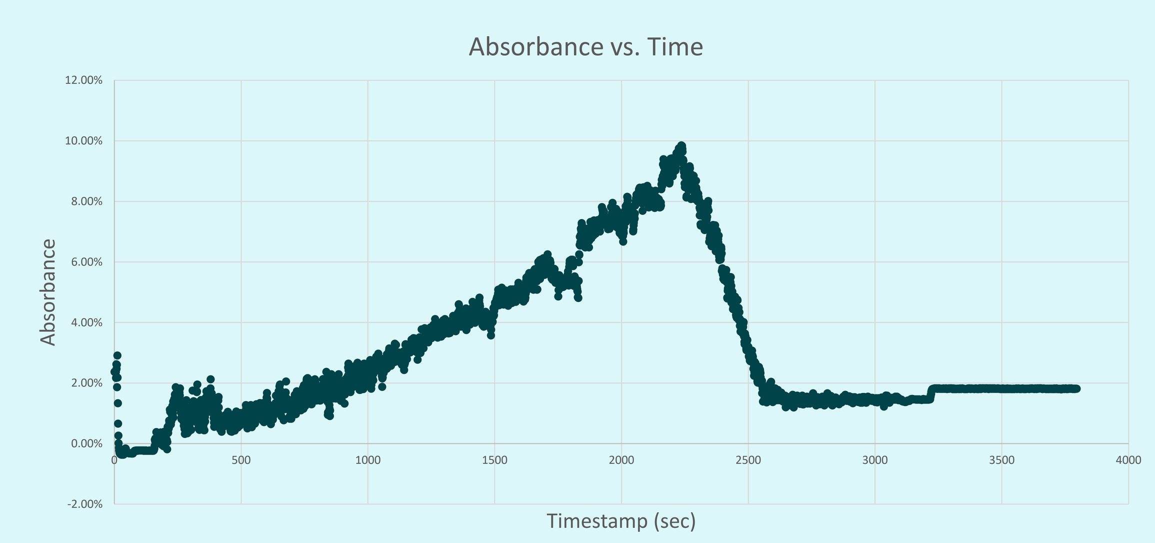


Figure 2: Raw data from the NIR filter photometer of absorbance vs. time

Material	Machine	ρB (g/cc)	ρT (g/cc)	Hausner Ratio	Carr's Index
Placebo (Ungranulated)	N/A	0.452	0.646	1.43	30.03
Placebo (Granulated)	VFC-15M	0.468	0.58	1.24	19.29
Placebo (Granulated)	VFC-60M	0.455	0.583	1.28	22.04
APAP (Ungranulated)	N/A	0.325	0.542	1.67	40.04
APAP (Granulated)	VFC-15M	0.419	0.499	1.19	16.03
APAP (Granulated)	VFC-60M	0.489	0.582	1.19	15.98

Table 1: Pre and Post Granulation Flowability Data

Particle sizes of both raw and granulated materials were also measured to show repeatability between trials using identical process parameters. For the granulated placebo batches, the D50 = 108.49±1.025um on the VFC-15M and D50 = 112.703±0.512um on the VFC-60M. While the VFC-15M D50 doesn't overlap with the VFC-60M D50 when factoring in the standard deviation, the percent difference is only 3.81%, which is still insignificant. With APAP, D50 = 347.18±6.837um on the VFC-15M and D50 = 353.437±16.877um on the VFC-60M, with the standard deviations for both machines encompassing the D50 of the other and the percent difference being only 1.79%. This demonstrates a very high level of repeatability between individual trials as well as the scaled-up process.

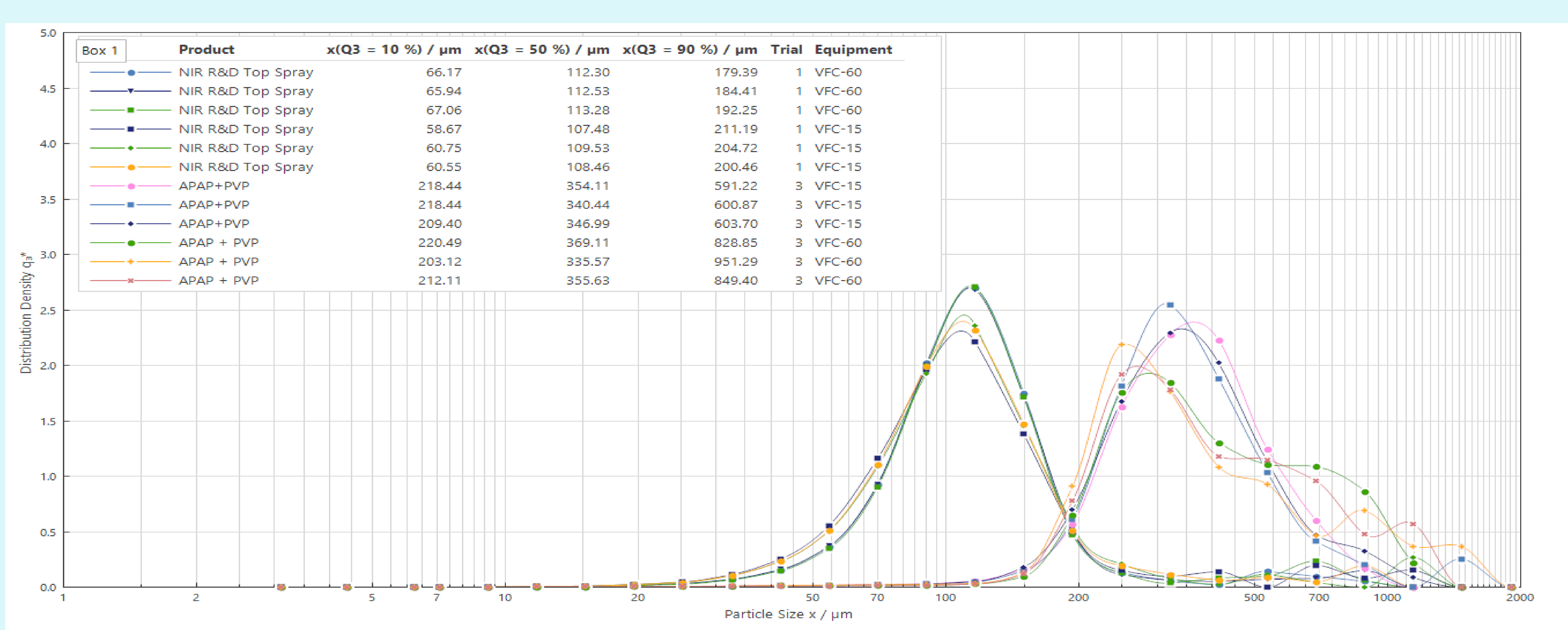


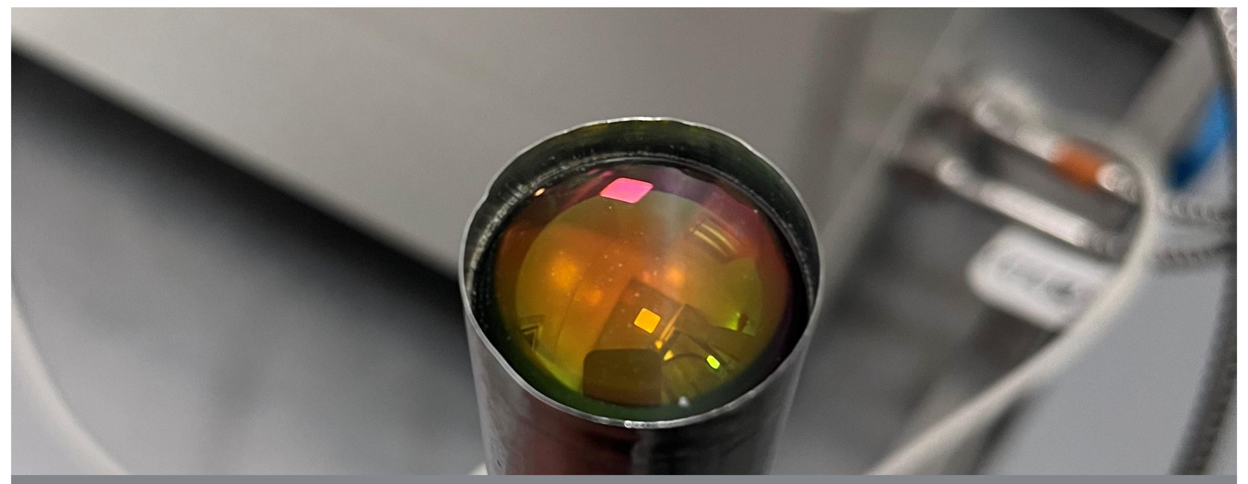
Figure 3: Particle size distribution of each final product on both the VFC-15M and VFC-60M

CONCLUSION(S)

NIR spectroscopy provided significant advantages over offline moisture measurement in terms of time required for sample analysis without a drop off in accuracy. This allows real time moisture data to be taken throughout the entire batch without the need for sampling the product and allowing for quicker responses to process upsets than would otherwise be possible with traditional offline moisture measurements.

NIR Photometer Mount on VFC-15M

NIR Photometer Mount on VFC-60M



NIR Filter Photometer

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