



Lactose particle size analysis using FT-NIR spectroscopy

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Introduction

In pharmaceutical analysis, chemical properties, efficacy, and purity are generally well defined, but physical properties such as particle size are often overlooked. Particle size can greatly affect the flowability and compressibility of the bulk raw material as well as dissolution, reaction rate, and tablet integrity. Confirming the particle size of raw materials ensures that the manufacturing process can be optimized to efficiently produce high-quality finished products.

The primary method for determining particle size in fine powders requires samples to be collected and passed through a jet sieve. Gravimetric analysis is then used to determine the percentage of the sample at any given mesh size. This requires samples to be taken to a QC lab for analysis, resulting in a loss of time and efficiency. A more optimal method of analysis would provide instantaneous results accurately without the need for a highly-skilled operator. The Thermo Scientific™ Antaris™ II FT-NIR Analyzer is an effective solution to determining particle size rapidly and accurately.

Near-infrared spectroscopy is based on combinations of vibrations and vibrational overtones that occur within organic molecules. Characteristic frequencies of NIR light are absorbed by molecules in the sample, initiating these specific vibrations. The remaining light is then collected by the analyzer and displayed as a spectrum. While chemical identification of the substance depends on the various peaks present in the spectrum, differences in physical properties of the material manifest themselves in baseline offsets and slopes. In the current application, we examine the effect of spectral pre-processing on the classification of different particle sizes of lactose, a common pharmaceutical excipient.

Experimental

Samples of pharmaceutical grade lactose monohydrate with mesh sizes ranging from 50 – 125 microns (Table 1) were obtained from DMV International (Veghel, Netherlands; sold under the brand name Pharmatose®). Ten samples of each were scanned with an Antaris II Method Development Sampling (MDS) FT-NIR system in the range between 4000 and 10000 cm^{-1} . The materials were placed on the Integrating Sphere module using a sample cup (see Figure 1). The resulting spectra were evaluated with Thermo Scientific™ TQ Analyst™ Software using a Discriminant Analysis method in order to classify the samples by particle size. The raw spectra, as well as first- and second-derivative data, were used during the Discriminant Analysis to determine the most appropriate spectral format.

Mesh size	Microns
50	300
80	177
110	137
125	130

Table 1.



Figure 1. Antaris II MDS FT-NIR Analyzer. The lactose samples were placed in the Spinning Sample Cup Holder on the Integrating Sphere module as shown. Diffuse reflection spectra were collected in the range between 4000 and 10000 cm^{-1} . Each mesh-size was sampled 10 times.

Example spectra are shown in Figure 2, demonstrating typical differences between various particle sizes of the same material.

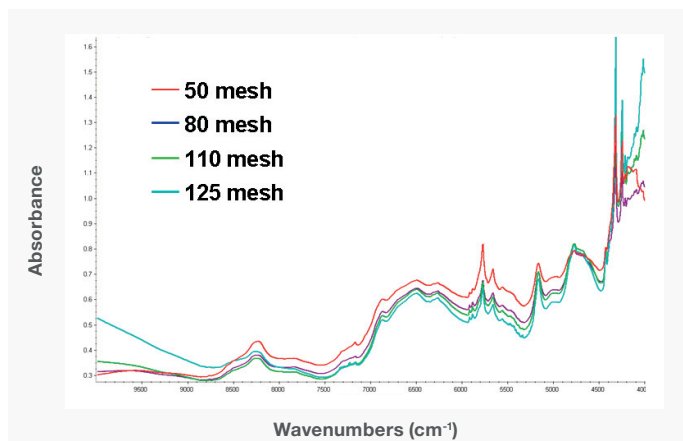


Figure 2. Representative spectra of the different, mesh-sized classes showing baseline offsets and differences in baseline slope.

Figure 3 shows comparisons between the first and second Principal Component (PC) scores for the raw spectra as well as for the derivative spectra. Principal Components describe the spectral variation in samples. The first PC describes the most variation, with each successive PC describing more of the remaining variation. A score value represents the multi-dimension distance of a sample in PC space. The PC score plot shows patterns or trends in the samples based on their PCs. The raw spectra Principal Component scores plot (Figure 3a) demonstrates excellent grouping and separation between the different particle size classes. This separation indicates that members of the different particle size classes can be discriminated from members of the other classes. Figure 3b shows a similar Principal Component scores plot for the first-derivative data. First derivatives remove baseline offsets. While the class separation in the Principal Component space has been somewhat reduced, good discrimination between the different classes is still evident. The second derivative scores plot is also included in Figure 3c. Second-derivative filtering removes sloping baseline effects. The Principal Component scores plot shows a degradation of the class separation, particularly with respect to 80 mesh (+) and 100 mesh (Δ).

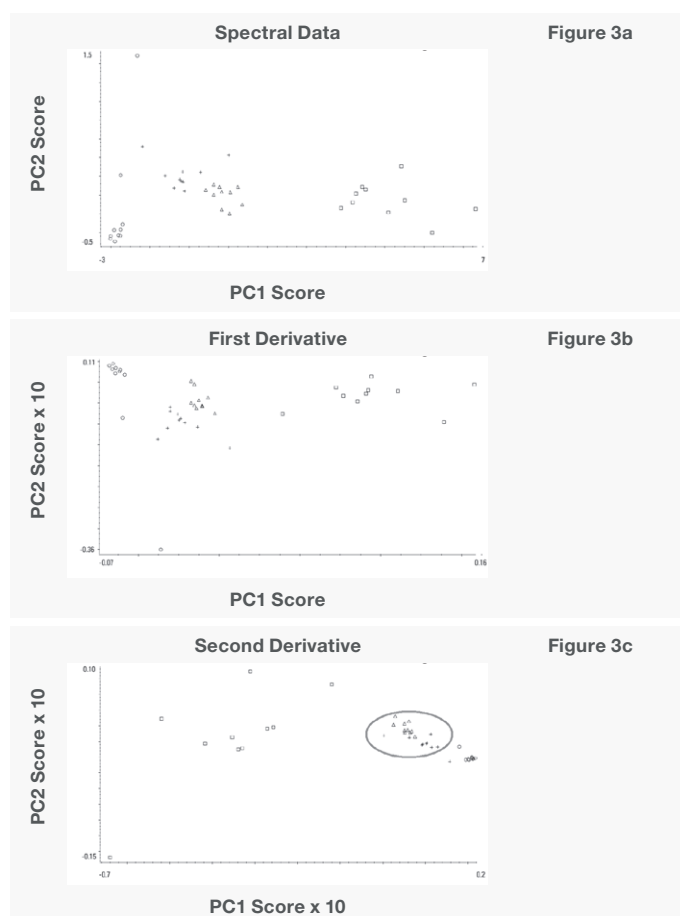


Figure 3. Principal Component score plots of raw spectra, as well as first- and second-derivative spectra. Different classes of lactose particles are well separated in the spectral data and sufficiently separated in the first derivative data. Second derivative shows less-defined separation, especially between the 80 mesh (+) and 100 mesh (Δ). Note circled region. 50 mesh is denoted with open circles (\circ); 125 mesh denoted by open squares (\square).

Mahalanobis distances were also calculated for the raw spectra as well as for the first- and second-derivative spectra. Mahalanobis distance is used in cluster analysis and can simply be described as a measure of the relative distance a particular point lies from the center of a cluster in Principal Component space. Larger Mahalanobis numbers indicate a particular spectrum or sample is less similar to the others in the cluster. Mahalanobis distances can also be used to classify sample spectra. A particular spectrum can have Mahalanobis distances calculated with respect to each of the classes, then that spectrum can be assigned to the nearest class, i.e., with the lowest Mahalanobis distance. Table 2 was constructed from the Mahalanobis distances of all of the samples using TQ Analyst Software. In this table, the distance from the nearest class was ratioed to the next-nearest class (incorrect class/correct class). This provides a means to compare how well a spectrum falls within its class versus how close it might be to an incorrect class. Larger numbers in Table 2 indicate a sample is well within its class and not likely to be misclassified to a different mesh size. The first derivative column in Table 2 has smaller ratios than the spectra column, indicating that the first derivatives are not as clearly separated into the correct classes. Furthermore, the second derivative data shows that several of the samples are “misclassified” in that they lie closer to an incorrect class than the actual class. This is indicated by ratios of less than one. This further demonstrates that physical properties such as particle size are detectable in the raw spectral data but tend to disappear in the derivative data.

Conclusions

Baseline shifts and slopes are typically eliminated during spectral analysis in order to analyze chemically relevant information. Using the Antaris II FT-NIR Analyzer, different particle size classes of the common pharmaceutical excipient, lactose, have been correctly determined. Using the raw spectral information instead of the first or second derivative produces the best results for correct classification.

Size	Spectra	1 st derivative	2 nd derivative
50	3.24	1.33	0.99
	5.18	1.84	1.27
	5.37	1.78	1.19
	5.49	1.75	1.22
	4.91	1.55	1.11
	9.87	4.06	1.27
	5.53	1.52	1.08
	4.69	1.40	0.98
	4.84	1.66	1.18
	4.32	1.63	1.14
80	5.16	2.39	1.46
	6.96	1.64	0.85
	6.58	1.60	1.02
	4.02	2.20	1.50
	7.61	1.76	1.22
	6.99	1.57	0.94
	5.20	1.77	1.42
	6.29	1.50	0.88
	7.09	1.16	0.49
	5.44	1.86	1.18
110	3.50	1.38	0.71
	4.96	2.02	0.93
	5.11	1.79	0.66
	4.47	1.72	0.99
	3.95	1.56	0.75
	3.76	1.38	0.46
	3.29	1.23	0.41
	4.01	1.43	0.54
	3.59	1.35	0.46
	3.72	1.35	0.36
125	17.54	5.66	4.12
	15.86	9.28	8.33
	18.86	5.36	4.05
	15.58	5.15	3.96
	6.58	3.39	2.17
	13.77	4.62	3.10
	22.22	5.97	4.71
	9.62	5.00	3.73
	11.88	6.05	5.41
	20.43	4.52	3.20

Table 2. Mahalanobis distance ratios. Mahalanobis distances between the nearest class and the next-nearest class were ratioed. Large values indicate a particular sample is well categorized within its class. First derivative data shows several samples are close to an incorrect class (ratio < 1.5, in yellow). Second derivative data show several samples are misclassified (ratio < 1, in red).

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