An Analysis of Carrier/API Association: Morphologically Directed Raman Microscopy to Characterize a Dry Powder Inhaler

Linda H. Kidder, Kenneth S. Haber, Janie Dubois, and E. Neil Lewis

Malvern Instruments • 7221 Lee Deforest Drive • Suite 300 • Columbia, MD 21046

INTRODUCTION

The particle size distribution of the active pharmaceutical ingredient (API) in a dry powder inhaler is critical to ensure pulmonary rather than oral deposition. Optical microscopy (automated or manual) is a commonly employed approach, but is suffers significantly from the inability to adequately distinguish between APIs and excipients, particularly for small particle sizes. This analytical problem requires a hybrid analytical approach, in which the size and shape of particles is determined by automated optical microscopy, but particle identification is unequivocally provided through robust spectroscopic analysis. This ensures that excipient particles are not mistakenly included in the ensemble of particles used to determine the API particle size distribution.

This paper presents results work in which automated visible microscopy is used to determine the particle size distribution of an Advair sample. This hybrid approach (Morphologi G3-ID, Malvern Instruments) automates a manual process - the search for API particles via microscopy, and couples that with a validatable chemical identification method – Raman spectroscopy.

Experimental Workflow of Morphologically Directed Raman spectroscopy

To measure the particle size distribution of the API only, these particles must be distinctly identified from the excipient particles also present in the formulation. The implementation of automated microscopy coupled with image analysis and Raman spectroscopy allows rapid measurement of all particles within a selected scan area. Many thousands of particles can be analyzed, avoiding the bias or subjectivity that is often associated with manual microscopy. For every particle detected, an image is recorded and a Raman spectrum can be collected. API and excipient particles can be unequivocally identified and their physical size and shape characteristics analyzed.

Assessing particle size distribution of API - Workflow

1) Perform Morphologi measurement 2) Collect Raman spectra of individual particles 3) Classify API based on Raman correlation score 4) Produce particle size of API particles

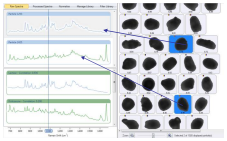

Figure 1: The Raman spectra of two individual particles, showing the ability of Raman to differentiate API and excipient particles. Reference spectra for the API and excipient are show in the green boxes.

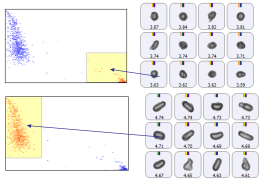

Figure 2: Scatterplots for Raman correlation scores of API vs excipient particles and examples of associated particle images for the two chemical classes. These data are from a Nasal Spray sample, and are for illustrative purposes only.

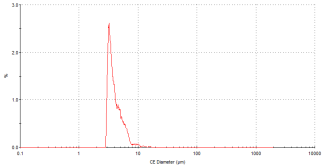

Figure 3: Particle size distribution of API particles based upon Raman spectroscopy. These data are from a Nasal Spray sample, and are for illustrative purposes only.

Particle Size Results

A comparative analysis between two Advair samples was performed. One powder sample was measured immediately after being removed from a sealed blister, the second was stored in a glass vial at ambient conditions for several months before being dispersed onto a standard mirrored slide and then measured.

The mean particle size for these two samples is quite similar, but the standard deviation in values across the distribution was significantly larger for the stored sample. Specifically, the maximum particle size of Fluticasone and Fluticasone/Lactose aggregates for the stored sample was significantly greater than the fresh sample.

	Fluticasone				*Salmeterol*				*Fluticasone/Lactose aggregates*			
	Num.	CE diam (µm)	Std Dev	Max (µm)	Num.	CE diam (µm)	Std Dev	Max (µm)	Num.	CE diam (µm)	Std Dev	Max (µm)
Fresh	249	3.8	1.4	9.1	7	2.8	1.3	6.6	135	5.2	1.4	10.78
Stored	207	3.7	6.7	95.0	5	2.7	0.8	3.7	29	6.5	3.6	21.67

Table 1: Particle size statistics of API particles based upon Raman spectroscopy for Advair samples. The Advair sample that had been stored at ambient conditions for several months exhibited a significantly large standard deviation of particles sizes for Fluticasone than the fresh sample. Additionally, the stored sample has a 95 micron maximum size particle, as well as 3 additional particles all over 10 micron in size.

Conclusions

- The addition of Raman spectroscopy enables the unequivocal determination of API particles, and therefore the API particle size distribution.
- A sample stored at ambient conditions for several months appears to have significant Fluticasone agglomeration.
- The use of automated system substantially reduces analysis time and subjectivity, enhancing the reproducibility of results.
- The impact of a variety of formulation and/or manufacturing parameters on the API particle size distribution could be efficiently studied.

Malvern Instruments Inc.
7221 Lee Deforest Drive • Columbia, Maryland • 21046
www.malvern.com

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