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Development and beyond: Strategy for long-term maintenance of an online laser diffraction particle size method in a spray drying manufacturing process

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ABSTRACT

The purpose of this manuscript is to present the intended use and long-term maintenance strategy of an online laser diffraction particle size method used for process control in a spray drying process. A Malvern Insitec was used for online particle size measurements and a Malvern Mastersizer was used for offline particle size measurements. The two methods were developed in parallel with the Mastersizer serving as the reference method. Despite extensive method development across a range of particle sizes, the two instruments demonstrated different sensitivities to material and process changes over the product lifecycle. This paper will describe the procedure used to ensure consistent alignment of the two methods, thus allowing for continued use of online real-time laser diffraction as a surrogate for the offline system over the product lifecycle.

1. Introduction

When the crystalline form of an active pharmaceutical ingredient (API) exhibits low solubility and low permeability, manufacture of an amorphous spray dried solid-dispersion (SDD) can be an effective solution for drug manufacture and delivery [1]. Spray drying can produce powders with reproducible particle size distributions (PSD), particle morphologies, and physical characteristics such as bulk density (BD) and surface composition, and has thus been identified as an effective process for targeted particle engineering [2]. For the drug product presented in this study, each of these attributes was important for downstream tablet performance and API release. Through a combination of empirically derived process control models and first-principles drying kinetics models, the manufacturing process was capable of reproducibly controlling each of these attributes from batch to batch. A series of experiments was run at-scale during early development in order to determine the relationships between SDD physical attributes and spray drying manufacturing variables such as condenser temperature, inlet/outlet temperature, nozzle orifice diameter, and feed pressure. In addition, solids load and raw material attributes were evaluated for their impacts on the SDD PSD.

The initial SDD particle size process control model consisted of an experimentally derived equation using the following inputs: feed pressure, outlet temperature, nozzle diameter, and solids load. Use of this equation allowed for the manufacture of highly reproducible PSDs as measured by two different instruments: (1) online Malvern Insitec, and (2) offline Malvern Mastersizer. The Insitec has been described previously for measuring PSD and concentration in air classification systems [3], monitoring maltodextrin microsphere particle size in a small-scale spray drying application [4], monitoring dry powder particle sizes during milling [5], and monitoring spray drying of oil-encapsulated microspheres [6]. To the authors' knowledge, the Insitec and the Mastersizer have not been used and compared for corresponding measurements. The control strategy was devised such that the online PSD measurement could serve as a surrogate in-process control measurement for the offline PSD measurement during manufacturing, and either technique could be used to test SDD throughout the process. The final reported particle size designated to represent the batch in its entirety was a single composite sample tested offline by the Mastersizer. As such, it was necessary that the two methods remain aligned throughout production across multiple batches to ensure consistent results, regardless of which technique performed the measurement.

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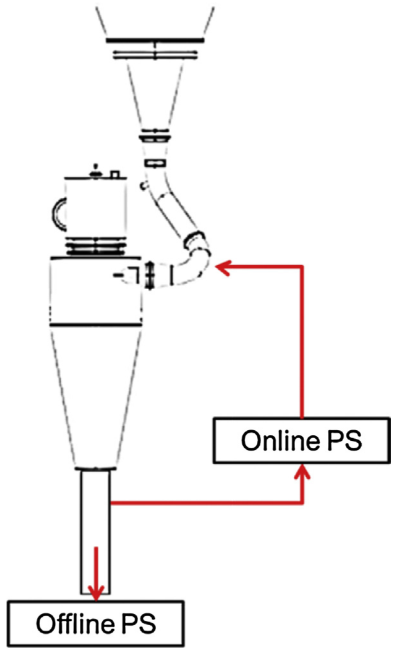

Fig. 1. Insitec configuration on the PSD4 spray dryer.

2. Experimental

2.1. Online particle size method and configuration in the spray dryer

The configuration for this particular installation is shown in Fig. 1. The Insitec instrument qualification was against a reticule (a glass-slide standard with fixed-gap markings), and was conducted with a fixed operational qualification schedule and/or when the system/configuration changed. Alignment and background were both verified prior to use in each manufacturing run. For comparison with the Mastersizer, as part of method validation, the Insitec bias and linearity were demonstrated across the measurement range with spray-dried dispersion. The Insitec used a 200 mm focal length lens (0.1 to 400 μm particle size) and a 90° venturi. Material was automatically sampled from the cyclone discharge chute and passed into a slip-stream recirculation loop. The slip-stream handling system was designed such that the SDD was presented to the Insitec at a consistent powder density and flow rate for every measurement within a batch as well as across batches. Dispersion energy was provided by the venturi, set to deliver a constant gas stream (9.5 N m^3/h). Table 1 shows the Insitec hardware and software configuration. Two system suitability criteria were established for determining an acceptable measurement value: (1) percent transmission ≤80%, and (2) number of counts at the scattering ring (channel 15) ≥500 counts. The first criterion ensured there was sufficient powder flow density for each measurement. When powder flow density was reduced through the optical path, there was an insufficient quantity of spray dried material presented to the Insitec for an accurate measurement. In practice, when the transmission values were higher than 80%, there were typically momentary blockages in the slip-stream prior to the measurement system. The second criterion was designed to ensure a minimum number of counts at the appropriate particle size. For the particle size of interest, channel 15 was selected as the gauge for laser scatter at the relevant particle size. In most cases, these two system suitability criteria passed or failed in tandem. The method was developed such that measurements were collected every 5 s, from which an 8-min moving average was calculated (96-points).

Table 1
Insitec configuration and instrument settings.

	Parameter	Value
Hardware	Online laser diffraction system	Insitec X
	Lens	200 mm (1–400 μm focal length)
	Venturi	90°
	Flow rate	9.5 Nm^3/h
Material settings	Model	Mie scattering
	Particulate refractive index	1.5 + 0.1i
	Media refractive index	1
	Particle density	1
Data analysis	Min particle diameter (μm)	0.1
	Max particle diameter (μm)	600
	Scattering threshold	8
	Multiple scattering	Yes
	First scattering ring	5
System suitability	Averaging	8-min
	Transmission	≥80%
	Counts at Sc(15)	≥500

The suitability criteria were applied to the 8-min moving average values, not the individual measurements. Therefore, it was often the case that multiple individual values did not meet the suitability requirements while the 96-point average was still well within specification.

2.2. Offline PS method

Particle sizes were measured offline with a Malvern Mastersizer laser diffraction instrument. The full scope of method development will not be addressed in this paper; however, highlights are presented in Table 2. A spray-dried dispersion dry powder measurement was performed and evaluated against a number of wet dispersants. For each of the wet dispersants, ultrasound was applied prior to measurement across the range from 0 to 5 min and a

Table 2
Mastersizer instrument settings.

	Parameter	Value
Instrument settings	Sample handling unit	Scirocco 2000
	Tray	General purpose
	Air pressure	1.0 bar
	Feed rate	75%
	Slit	Target: 5 mm, Range: 4–7 mm
Measurement options	Sample material name	Fraunhofer
	Refractive index	0.0
	Absorption	0
	Dispersant name	Air
	Refractive index of the dispersing agent	1.0
Result calculation	Model	General purpose (fine)
	Calculation sensitivity	Normal sensitivity
	Range	0.02–2000 μm
Sample options	Sample measurement time	20 s (20,000 snaps)
	Background measurement time	10 s (10,000 snaps)
	Aliquot per run	1
	Number of measurements per aliquot	1
	Obscuration limits	1–10%