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Analytical method development of the Particle size distribution methodology for Exemestane API

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ABSTRACT: Background: Exemestane is a drug used to treat breast cancer in women who have gone through the menopause. Its biological half life is 24 h. **Aim:** An experimental method was established for the measurement of the particle size distribution of Exemestane API using laser particle size analyzer. **Method:** A Malvern Mastersizer 3000 analyzer and Aero S (Dry mode) assembly were used. In this paper, the influences of refractive index, Particle type, Air pressure feed rate, Slit width and measurement time of the particle size distribution of Exemestane were systematically studied. **Results:** The instrument condition were as follows that are, Air pressure: 3.8 bar, Feed rate: 95 %, Slit width 1.5, measurement time for background and samples 10s, sample refractive index 1.572, and sample absorbency 0.01. **Conclusion:** The method is accurate, simple, repeatable and suitable for the particle size analysis of Exemestane over the wet method of analysis.

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INTRODUCTIONS:

Within the pharmaceutical industry, the particle size distribution (PSD) of an active pharmaceutical ingredient (API) may have a significant impact on both the manufacturability (flowability, packing properties, mixing, etc.) and quality attributes of the drug product (dissolution rate, bioavailability, content uniformity, etc.) Throughout drug development, it is important to understand how particle size of an API impacts drug product performance and manufacturability especially for BCS class 2 & 4 category of API; therefore, an appropriate analytical method is required for obtaining quantitative information on particle size distribution [1].

Particle size is a critical quality attribute for a diverse array of pharmaceutical products, from topical ointments to powders for pulmonary delivery. During recent decades, the unique attributes of laser-diffraction analysis have positioned it as the particle-sizing technique of choice for the resulting spectrum of pharmaceutical applications. Fast, nondestructive and suitable for a broad size range (0.1 to 3000 μm), laser diffraction lends itself to full automation [1].

Mastersizer 3000 Sample Dispersion Overview [1]:

Sample dispersion is controlled by a range of wet and dry dispersion units. These ensure the articles are delivered to the measurement area of the optical bench at the correct concentration and in a suitable, stable state of dispersion to make accurate and reliable particle size measurements.

Aero – Redefining Dry Powder Dispersion [2]:

Setting new standards for dry powder dispersion, the Aero has been designed from the ground up based upon fundamental powder dispersion theory.

The modular design ensures rapid and reproducible dispersion of cohesive powders for both fragile and more robust materials.

The Aero is available with two performance levels:

Aero M - entry-level, manually-operated dry powder dispersion unit for use with the Mastersizer 3000E.

Aero S - fully automated dry powder dispersion unit for the Mastersizer 3000, designed with the flexibility to meet the widest possible range of applications.

Hydro - Rapid and Effective Wet Dispersion Accessories [3]:

Hydro LV - A large volume automated dispersion unit suitable for applications where sample availability is not an issue or where larger volumes are required to ensure good sampling.

Hydro MV - A medium volume automated dispersion unit specifically designed for applications where sample is in short supply and/or non-aqueous dispersants are necessary.

Hydro Sight **-** A lens-less dynamic imaging accessory, supporting method development and troubleshooting by providing real time visualization and assessment of liquid particle dispersions.

Hydro SV - A small volume dispersion unit designed to enable particle size analysis when dispersant use needs to be minimized or the amount of sample available for analysis is limited.

Hydro EV - A unique dip-in, semi-automated wet sample dispersion unit that can be used with 250mL, 600mL and 1000mL standard laboratory beakers.

Hydro SM - Entry level medium volume sample measurements, suitable for applications where samples need to be dispersed in non-aqueous dispersants.

The principles of Mastersizer (Laser diffraction) [4]:

Understanding the basic principles of laser diffraction is essential for successful method development. Laser diffraction is an ensemble particle-sizing technique, which means it provides a result for the whole sample, rather than building up distributions from data for individual particles, in the way that, for example, image analysis or microscopy does. Particles illuminated in a collimated laser-beam scatter light over a range of angles. Large particles generate a high scattering intensity at relatively narrow angles to the incident beam, while smaller particles produce a lower intensity signal but at much wider angles. Using an array of detectors, laser-diffraction analyzers record the pattern of scattered light produced by the sample.

The Mastersizer range of laser diffraction particle size analyzers set the standard for delivering rapid, accurate particle size distributions for both wet and dry dispersions. From assessing product uniformity and solubility, through to optimizing packing density to improve final product performance and controlling powder flowability to increase manufacturing efficiency, particle size analysis is critical to understanding and controlling a wide range of properties.

In a laser diffraction measurement a laser beam passes through a dispersed particulate sample and the angular variation in intensity of the scattered light is measured. Large particles scatter light at small angles relative to the laser beam and small particles scatter light at large angles.

The angular scattering intensity data is then analyzed to calculate the size of the particles that created the scattering pattern using the Mie theory of light scattering. The particle size is reported as a volume equivalent sphere diameter.

Mastersizer 3000:

A completely new optical core design delivers fast measurement times for high sample throughput and a measurement size range from 10 nm to 3.5 mm. Combined with a range of wet and dry dispersion accessories this opens up more applications than ever before.

The Mastersizer 3000 uses the technique of laser diffraction to measure particle size distributions from 10 nm up to 3.5 mm [4].

Aero S Dry Powder Disperser:

The Aero S is a completely new dry powder disperser developed using state-of-the-art powder dispersion understanding. Modular in design, it is easily configured for different applications, delivering efficient sample dispersion for both robust and fragile materials.

Standard disperser suitable for both cohesive and fragile particle measurements. Impaction systems available for robust material dispersion. Precise dispersion pressure control, to ±0.1 bar delivers outstanding reproducibility. Range of sample feed trays and hoppers enable measurement of different sample volumes. Enclosed cell delivers bias-free measurements whilst minimizing user exposure to the sample. Full software control of all measurement functions, including sample feed and dispersion. Ceramic dispersers available for abrasive materials [5].

Principle of Dry method (Aero S):

Dry measurement of particle size is fast and removes the need for liquid dispersants. It is the best method for many dry powders, and is especially important when particle size is influenced by hydration. The Aero S disperses dry samples by accelerating particles through a venturi using compressed air. The particles are then pulled through the Mastersizer 3000's measurement cell using a vacuum source.

Dispersion efficiency is controlled by three variables: air pressure, sample feed rate and disperser geometry.

Mechanisms of dry powder dispersion: Representative measurement relies on providing sufficient energy to break up agglomerates without causing primary particle damage. Dry powder dispersers accelerate particles in an airstream to achieve this.

With dry powder dispersion there is always the possibility of particle damage, because of the high velocity at which the particles pass through the disperser system. The unique design of the Aero S minimizes this problem by avoiding impaction surfaces. Dispersion is achieved through the application of significant shear, rather than by impacting particles on a surface. The result is gentle but highly efficient dispersion, which can be successfully applied to even relatively friable materials. Optional impaction systems are available for strongly agglomerated samples with tough primary particles. The air pressure drop across the venturi is manipulated to achieve complete sample dispersion and can be controlled to within +/-0.1 bar [6]. Sample feed rate through the Aero S is closely controlled using a vibrating feeder, which maintains a suitable sample concentration for measurement. It is fitted with an interchangeable sample tray that can be configured to ensure the measurement of enough material to quantify the entire size distribution reproducibly.

Because of its high data acquisition rate, the Mastersizer 3000 samples the dispersed material very efficiently, even though material passes through the measurement cell quickly. This increases the measurement robustness, and accelerates analysis [6]. In combination, these features deliver reliable, reproducible dispersion for the very widest range of dry samples.

Technical specification of Aero S:

Particle size: 0.1 - 3500 µm

Dispersion pressure range: 0 - 4 bar

Pressure setting precision: +/- 0.1 bar

Pressure setting accuracy: +/- 0.03 bar

Feed rate range: 0 - 58ms-2 (expressed as 0-100 %)

Feed rate precision: 2 % FS

Materials in contact with the dispersant, additives and sample: 316 stainless. 410 hardened stainless. Borosilicate glass. EPDM, PTFE. Polyurethane. Carbon filled acetal. Aluminum. Neoprene.

Maximum particle size: 3500 µm

Minimum particle size: 10 nm

Minimum time between measurements: Less than 60 s

Dimensions (W, D, H): 180mm x 260mm x 380mm

Weight: 10.5 kg

Power: Supplied via the optical unit.

Sample dependent.

MATERIALS AND METHODS:

Malvern Mastersizer 3000 equipped with Aero S accessory and Mastersizer software version no. 1.70 was used available at Oman Pharmaceutical Products L.L.C. Exemestane API manufactured by Symbiotica Speciality Ingredients SDN. BDH, Malayasia was used for the method development purpose.

Malvern Mastersizer 3000:

The instrument setup of Malvern Mastersizer is given in Table 1.

Particle size analysis:

Particle size determination was performed as per the methodology in six replicate preparation of Exemestane API and it was measured using the Malvern Mastersizer

3000 Aero S instrument. Add sufficient quantity of the sample in the dry powder feeder. Enter the parameters and determine the particle size of the test sample. The powder feeder and hopper were cleaned after each measurement.

Table 1. Instrumental setup.

Instrument & Model	Malvern – Mastersizer 3000
Accessory	Aero S (Dry Mode)
Analysis Model	General purpose
Sensitivity	Normal
Size range	0.1 to 3500 µm

Table 2. Product parameters.

Material Name	Exemestane API
Material Refractive	1.572
Absorption Index	0.01
Particle density	1.13 g/cm3

Table 3. Instrumental parameters.

Venturi type	High energy venturi disperser
Tray type	General purpose tray (with hopper)
Particle type	Opaque particle (Fraunhofer Approx.)
Slit width (mm)	1.0 mm
Analysis model	Narrow modes
Vibration feed rate	95 %
Air pressure	3.8 barg
Measurement snaps	1
Background measurement duration (s)	10 s
Sample measurement duration (s)	10 s
Obscuration low limit (%)	1.00 %
Obscuration high limit (%)	10.00 %

RESULTS AND DISCUSSION:

The % RSD and the results observed were well within the acceptance criteria. The Table 4 and 5, indicates the method was precise, reproducible and confirms the verification of methodology.

CONCLUSION:

The dry method developed and verified for the determination of particle size for Exemestane API was found to be accurate, simple and economical over the wet method of analysis using surfactant. Hence, this method can be used for the routine analysis of Exemestane API particle size determination. The following precautions shall be taken into care of like Never look into the direct path of the laser beam or its reflections, Earth all instrument components to prevent ignition of solvents or dust explosions and Check the instrument setup (e.g., warmup, required measuring range and lens, appropriate working distance, position of the detector, no direct bright daylight).

Table 4. Acceptance criteria and Results.

Method	NSS	Specification	NMV DMA	RVWMA
Particle size determination	6 sample determination	d_{10}: NMT 1 µm	0.8	0.4
		d_{50}: NMT 3 µm	2.8	2
		d_{90}: NMT 7 µm	6.0	5

NSS - No of samples set, NMVFDMOA - New method values from Dry mode of analysis, RVWMA - Reference values from Wet mode of analysis.

Table 5. PSD results of the Particle size distribution methodology for Exemestane API.

Trial No	d_{10}	d_{50}	d_{90}
1	0.788	2.81	5.95
2	0.789	2.88	6.11
3	0.782	2.84	6.05
4	0.799	2.81	5.87
5	0.786	2.85	5.94
6	0.784	2.89	6.04
Avg	0.8	2.8	6.0
SD	0.00612	0.0328	0.0866
RSD	0.8	1.2	1.5

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Fig 1. Aero M Instrument.

Fig 2. Aero S Instrument.

Fig 3. Hydro LV Instrument.

Fig 4. Hydro Sight Instrument.

Fig 5. Hydro EV instrument.

Fig 6. Hydro SV instrument.

Fig 7. Hydro EV instrument.

Fig 8. Hydro SM instrument.

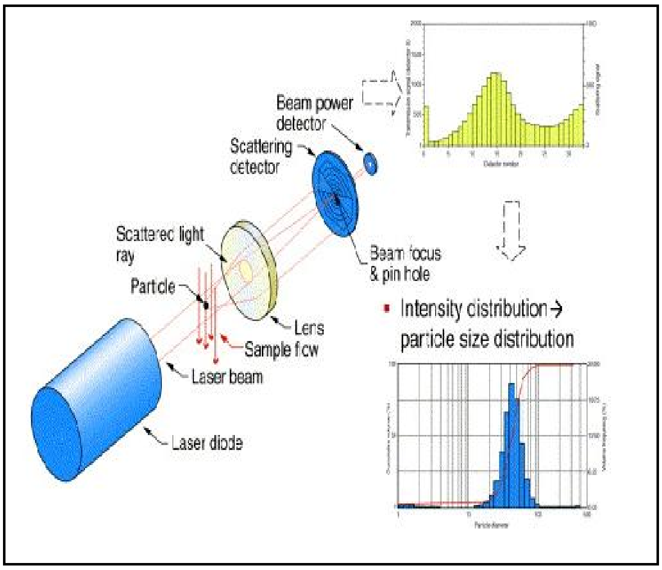

Fig 9. Working Principle of instrument for particle size analysis.

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