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Validation of Particle Size Distribution methodology for Clarithromycin API using Laser based particle size analyzer

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ABSTRACT: Background: Clarithromycin is an antibiotic used to treat various bacterial infections. This included strep throat, pneumonia, skin infections, H. pylori infection, and Lyme disease, among others. **Aim:** Clarithromycin has the characteristic nature of lump formation and determination of particle size with reproducible results is difficult and the particle size determination method is not reported in the literature. Hence novel rugged and reproducible methods have been developed for the determination of particle size distribution of Clarithromycin. The dry method using Aero S has been developed and validated as per the International Conference on Harmonization guidelines (Q2R1) and found robust and reproducible with % RSD of d(10), d(50), and d(90) values found within acceptance limit ranges from 15 % for d(10), 10 % for d(50) and 15 % for d(90) in validation. **Method:** An experimental method was established for the measurement of the particle size distribution of Clarithromycin API using a laser particle size analyzer. 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 Clarithromycin were systematically studied. The instrument condition is as follows: Air pressure: 1.1 bar, Feed rate: 40 %, Slit width 1.0, measurement time for background and samples 10 s, and sample refractive index 1.500**. Result:** The method is accurate, simple, repeatable, and suitable for the particle size analysis of Clarithromycin over the wet method of analysis. **Discussion:** The developed method was validated according to ICH guidelines and values of accuracy, precision, and other statistical analysis were found to be in good accordance with the specified acceptance criteria. **Conclusion:** The proposed method was successfully applied for the determination of particle size distribution of Clarithromycin API for routine analysis.

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INTRODUCTION:

Clarithromycin (Fig 1) is used to treat a wide variety of bacterial infections. This medication can also be used in combination with anti-ulcer medications to treat certain types of stomach ulcers. It may also be used to prevent certain bacterial infections. Clarithromycin is known as a macrolide antibiotic. It works by stopping the growth of bacteria. It does not work for viral infections (such as the common cold, and flu) [1].

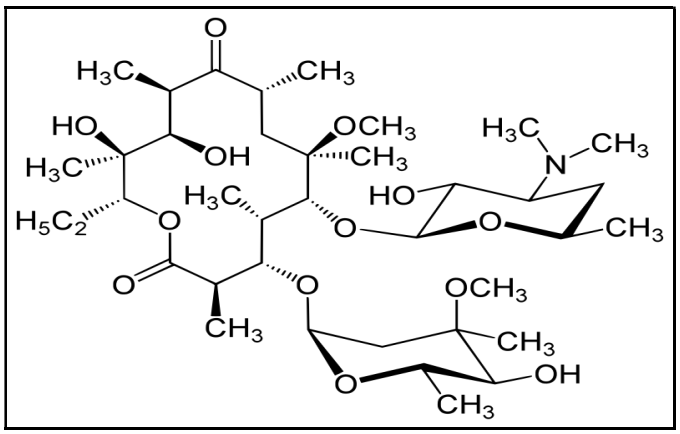

Fig 1. Structure of Clarithromycin.

To reduce the development of drug-resistant bacteria and maintain the effectiveness of Clarithromycin tablets and other antibacterial drugs, Clarithromycin tablets should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy [1,2].

Clarithromycin tablets are indicated in adults for the treatment of mild to moderate infections caused by susceptible isolates due to *Haemophilus influenzae*, *Haemophilus parainfluenza*, *Moraxella catarrhalis*, or *Streptococcus pneumonia* [3].

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 the particle size of an API impacts the drug product performance and manufacturability, especially for the BCS class 2 and 4 categories of API. Therefore, an appropriate analytical method is required for obtaining quantitative information on particle size distribution [4,5].

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, non-destructive, and suitable for a broad size range (0.1 to 3000 µm), laser diffraction lends itself to full automation [6].

The objective of the current study was to develop a simple, rapid, and cost-effective particle size methodology for Clarithromycin drug substance without the use of any hazardous organic solvents [7].

MATERIALS AND METHODS:

Malvern Mastersizer 3000 equipped with Aero S accessory and Mastersizer software version no. 1.70 available at Oman Pharmaceutical Products L.L.C. was used for the analytical method validation. Clarithromycin API manufactured by Ind-Swift Laboratories was used for this study.

Particle size determination:

Particle size determination was performed as per the methodology in six replicate preparations of Clarithromycin API and is measured using the Malvern Mastersizer 3000 Aero S instrument as mentioned in the Table 1. For the validation of Particle Size Distribution methodology for Clarithromycin API, the parameters that are Precision, Ruggedness, and Accuracy were studied.

Table 1. The Instrumental setup for the particle size analysis.

Instrument	**Laser Scattering particle size distribution analyzer**
Make	Malvern
Model	Mastersizer 3000
Handling Unit	Aero S
Material R.I	1.500
Material Absorption	0.0
Particle density	1.20
Feed rate	40 %
Air pressure	1.1 barg
Analysis Model	Narrow Modes
Fine Powder mode	ON
Venturi type	Standard venturi disperser
Particle Shape	Spherical shape
Measurement type	10 s (10000 Snaps)
Background	10 s (10000 Snaps)
Obscuration Range	1 to 10 %
Tray type	General purpose tray (with hopper)
Hopper gap	1.0 mm
No. of Measurement's	1

RESULTS AND DISCUSSION:

The % RSD and the results observed are well within the acceptance criteria.

Method Precision:

Precision of the method was determined by running the sample as per above method in six replicas and recording the particle size of d(10), d(50), and d(90). Finally, the % RSD of the particle size results obtained at d(10), d(50), and d(90) was deduced. The data obtained for the six sample preparations have been presented in Table 2 and Fig 2.

Table 2. Precision Study data.

Sample	Dx 10µm	Dx 50µm	Dx 90µm
1	22.5	96.8	223
2	22.6	96.8	223
3	22.7	96.7	221
4	22.4	95.7	219
5	23.3	98.2	223
6	23.0	97.8	221
Mean	22.8	97.0	222
SD	0.339	0.888	1.633
%RSD	1.5	0.9	0.7

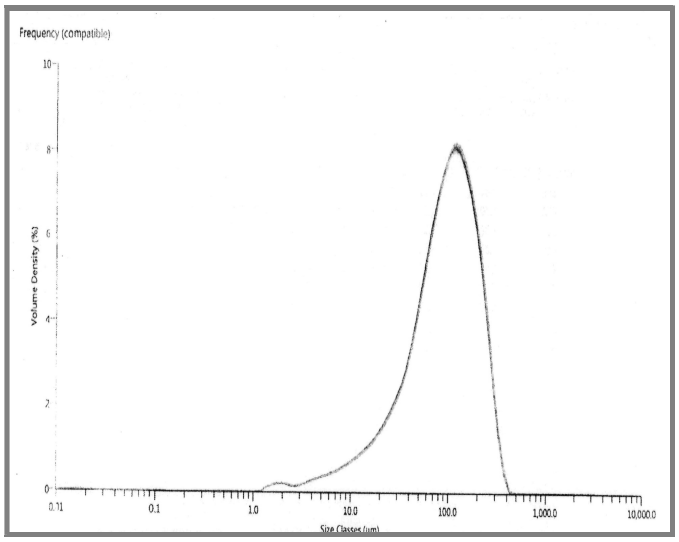

Fig 2. Reference Histogram of Sample Solution.

Ruggedness:

Ruggedness of the method was demonstrated by running the sample as per the method in six replicates by a different analyst on a different day and recording the particle size for d(10), d(50), and d(90). Finally, the % RSD of the particle size results obtained at d(10), d(50), and d(90) was deduced. The data obtained for the six sample preparations have been presented in Table 3.

Table 3. Intermediate Precision Study.

Sample	Dx 10 µm	Dx 50 µm	Dx 90 µm
1	24.3	101.0	229
2	24.1	99.4	225
3	23.9	99.2	224
4	23.6	97.6	218
5	22.2	88.7	210
6	21.0	82.0	192
Mean	23.2	94.7	216
SD	1.304	7.586	13.633
%RSD	5.6	8.0	6.3

Accuracy:

Accuracy of the method was concluded by comparing the PSD results of analysis obtained at Oman Pharmaceutical Products vis-à-vis the results reported by Ind-Swift Laboratories in the COA for the same batches. The data obtained for the accuracy study have been presented in Table 5.

In the procedure, enough of the sample was added in the dry powder feeder. The parameters were entered and the particle size of the test sample was determined.

CONCLUSION:

The analytical method validation for Particle size of Clarithromycin API by Particle size analyzer (Dry dispersion) was carried out by performing the parameters Precision, Intermediate Precision and Accuracy. All the data has been compiled and found to be satisfactory. Hence, the proposed method is economical, simple, ultra-fast, sensitive, and reliable and is found to be accurate, precise, specific, and rugged. All these parameters considered for validation meet the predefined acceptance criteria. Hence, this method can be used for the routine analysis of Clarithromycin API particle size determination.

Few precaution need to be adopted while handling the instrument that are 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., warm-up, required measuring range and lens, appropriate working distance, position of the detector, no direct bright daylight).

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Table 4. Precision and Intermediate comparison.

Sample	Dx 10µm		Dx 50µm		Dx 90µm	
SET	Precision	Intermediate Precision	Precision	Intermediate Precision	Precision	Intermediate Precision
1	22.5	24.3	96.8	101.0	223	229
2	22.6	24.1	96.8	99.4	223	225
3	22.7	23.9	96.7	99.2	221	224
4	22.4	23.6	95.7	97.6	219	218
5	23.3	22.2	98.2	88.7	223	210
6	23.0	21.0	97.8	82.0	221	192
Mean	22.8	23.2	97.0	94.7	222	216
SD	0.339	1.304	0.888	7.586	1.633	13.633
%RSD	1.5	5.6	0.9	8.0	0.7	6.3
Cumulative mean	23.0		95.8		219.0	
SD	0.936		5.293		9.667	
%RSD	4.1		5.5		4.4	

Table 5. Accuracy Study data.

Sample	Dx 10µm		Dx 50µm		Dx 90µm	
SET	**OPP**	**IND-SWIFT**	**OPP**	**IND-SWIFT**	**OPP**	**IND-SWIFT**
1	22.5	33.0	96.8	88.0	223	188
2	22.6	-	96.8	-	223	-
3	22.7	-	96.7	-	221	-
4	22.4	-	95.7	-	219	-
5	23.3	-	98.2	-	223	-
6	23.0	-	97.8	-	221	-
Mean	22.8	33.0	97.0	88.0	222	188.0
SD	0.339	-	0.888	-	1.6330	-
%RSD	1.5	-	0.9	-	0.7	-
Cumulative mean	24.2		95.7		217	
SD	3.886		3.497		12.812	
%RSD	16.1		3.7		5.9	

development and validation for particle size determination of Clarithromycin API by dry mode.

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