WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.084
Volume 11, Issue 12, 1457-1465. Research Article ISSN 2277– 7105

DEVELOPMENT AND VALIDATION OF NOVEL ANALYTICAL METHOD FOR THE DETERMINATION OF PARTICLE SIZE DISTRIBUTION IN LUMEFANTRINE USING LASER-BASED PARTICLE SIZE ANALYZER

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Article Received on
30 June 2022,

Revised on 20 July 2022,
Accepted on 10 August 2022

DOI: 10.20959/wjpr202212-25299

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ABSTRACT

The particle size distribution of Lumefantrine method development and subsequently validation was carried out by using the Malvern Instrument equipped with laser diffraction techniques. The method was developed by optimizing the instrumental parameter along with the optical parameter. Particle size is the key factor for modern drug quality since it affects the bioavailability and dissolution profile of the drug product. A study on Particle size is helpful to optimize the drug product development process and improve the quality of drugs. An Innovative and precise Particle size determination method has been developed for the determination of particle size distribution of Lumefantrine was described in this paper. This method has shown good reproducible results. By using water as a dispersant wet method is developed. Validation is performed as per the International Conference on Harmonization guidelines (Q2 (R1) and found robust and reproducible with % RSD of d (10), d (50), and d (90) values found within the acceptable limit invalidation. The described method is precisely developed and validated successfully and applied for the determination of particle size distribution of Lumefantrine. The particle size method is discussed in detail to ensure an in-depth understanding of particle size distribution and said method can be used for particle size determination of Lumefantrine. The method was validated for Precision, Intermediate Precision, and Robustness.

KEYWORDS:- Lumefantrine, Method Development, Method Validation, and Particle size analyzer (PSA).

1.0 INTRODUCTION

The Lumefantrine compound is yellow powder. It is an antimalarial drug used in combination with the artemether for the treatment of multi-drug resistant strains of falciparum malaria.[1] It has a role as an antimalarial. It is a tertiary amine, a member of monochlorobenzenes, secondary alcohol, and a member of fluorenes. It is chemically, 2, 7-Dichloro-9-[(4-chlorophenyl) methylene]-α- [(dibutyl amino) methyl]-9H-fluorene-4-methanol[2] The compound is a yellow powder that is poorly soluble in water, oils, and most organic solvents, but soluble in unsaturated fatty acids and Acidified organic solvents.[3,4] Lumefantrine is extensively Bound (≈99%) to plasma proteins, mainly high-density Lipoproteins (Colossi D et al., 1999). The molecular structure has been presented in fig 1.[5,6]

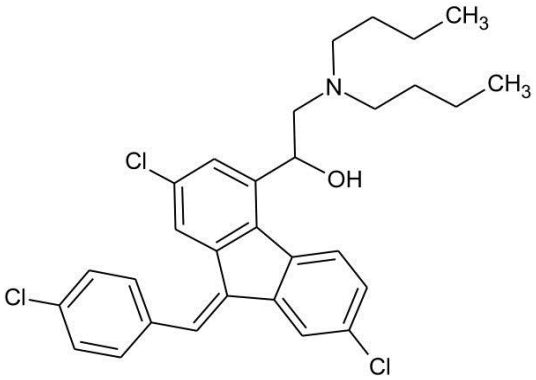

Figure 1: Chemical structure of lumefantrine.

Particle size reduction is a fast and gainful answer to increasing the exposure of poorly soluble oral drugs by increasing surface area and thereby improving the dissolution rate. Particle size analysis has become an indirect means for routine surface area measurement. Lumefantrine particle size determination literature survey was done and found that the Particle size determination method is not available and no adequate work is done on a said molecule for particle size determination. To determine the quality of these important drug substances, it is important to have an accurate method for the analysis of the Particle size distribution of Lumefantrine. Therefore the study was carried out to establish a method to determine the particle size distribution of Lumefantrine by particle size analyzer.

It was found that Water is a well-suitable dispersant for better suspension, and also the method developed by using the water as a dispersant is rugged and further validation for the precision and intermediate precision.[7] All the particle size data has been compiled and found to be satisfactory, Hence the method is suitably used for the analysis of the Particle size analyzer of Lumefantrine active pharmaceutical ingredients.

2.0 MATERIAL AND INSTRUMENTS

2.1 Chemicals

Lumefantrine Active Pharmaceutical Ingredient, Tween -20, Isopropyl alcohol, Milli-Q Water, Toluene, and Cyclohexane.

2.2 Instrumentation

Malvern (2000) system was used for Particle size method development and validation, equipped with Hydro accessories (2000S), Mastersizer Software (Version-5.61) was used for data processing and evaluation.

3.0 RESULT AND DISCUSSION

3.1 Analytical method development

The main objective was to develop the method to obtain the most stable, reproducible, and consistent method. To develop the method, a dispersant is played a critical role, dispersant should be selected by studying solubility where Lumefantrine should be insoluble in the selected dispersant and form uniform suspension. Various dispersants like Toluene, Cyclohexane, and n-Hexane are used for the solubility, the drug product is soluble in the mentioned dispersant hence it's not suitable for the further developmental activity, so for a few more dispersants checked, it was observed that drug product is insoluble in isopropyl alcohol as well as in water. Water is selected based on availability and costs.

Transferred 100.26 mg of sample in the beaker and a few drops of dispersant isopropyl alcohol. And make a paste by using a glass rod, then add 20 mL of dispersant. Sonicate externally for 1 minute to form a homogeneous solution with uniform suspension.

First used isopropyl alcohol as a dispersant for the method development and instrument parameter is kept as, Equipment Malvern Mastersizer, Model- Mastersizer 2000 which uses 52 detectors array, Sample handling unit- Wet Dispersion Unit- Wet Dispersion Unit, Sample model- Hydro 2000S, Dispersant name- Isopropyl Alcohol, Dispersant refractive index-1.390, Sample refractive index-1.633, Sample absorption-0.1, Sample measurement time-10 second, Measurement Snaps-10,000, Background Measurement time-10 second, Background Snaps-10,000, Obscuration range- 10-30%, Stirrer speed-2000 rpm, No. of measurement cycle-03, Create average of three measurement cycle.

From the above method, the result was produced as d (10) µm, d (50) µm & d (90) µm was 18.686, 42.390 & 77.709 respectively but the obscuration value is gradually decreasing. So this dispersant was ruled out. Tried for the water as a dispersant, it was found that it's well suitable dispersant for the better suspension to added few drops of Tween-20 to get the uniform suspension to develop a method for determination of particle size distribution of Lumefantrine.

The sample was prepared by transferring 100.26 mg of sample in a beaker adding 1-2 drops of Tween-20 and a few drops of dispersant water and making a paste by using a glass rod, then adding 20 mL of dispersant. Sonicate externally for 1 minute to form a homogeneous solution.

After sample preparation proceeded for trial by keeping all method parameters the same as used in the isopropyl alcohol method and only change in dispersant water and its refractive index of water instead of Isopropyl alcohol. Sample analysis was performed and results were obtained as d (10) µm, d (50) µm & d (90) µm was 3.793, 29.197 & 63.608 respectively. The obscuration, weighted residual, and Concentration are well within the limit proving that optical property is well suited for the product. Hence, from the above trial, it's observed that water as a dispersant method is suitable for analysis and further confirmed by reproducibility and % RSD of d(10), d(50), and d(90) results are satisfactory. Hence this method was further checked for reproducibility of Lumefantrine particle size distribution.

For the Repeatability, test samples were prepared, and subsequently, analysis was performed in triplicate to check reproducibility. Obtained average results of Repeatability-1 Repeatability-2, & Repeatability-3, as d (10) µm, d (50) µm & d (90) were 4.106, 27.864 & 57.983 and its % RSD 8.89%, 5.93% & 6.25%.respectively.

The results obtained in the repeatability with water as dispersant d(10), d(50), and d(90) values were found reproducible, and % RSD of the same was well within the general criteria of USP, General Chapter <429>.

3.2 Method validation

The validation work was conducted according to the ICH (International Conference on Harmonization) guidelines Q2R1. The method was validated for Precision, Intermediate Precision, and Robustness.

3.2.1 Method Precision & Intermediate precision

% RSD of Lumefantrine during the study of the precision and intermediate precision was within the limit. In the study of the precision and intermediate precision cumulative average and cumulative percent relative standard deviation for particle size at d (10), d (50) & d (90) of twelve measurements were within limit. The results are shown and confirming the robustness of the method.

Table no. 1

Parameter	Measurement No.	d (10)	d (50)	d (90)
Method Precision	Measurement-1	5.666	30.984	82.559
	Measurement-2	5.042	34.191	80.785
	Measurement-3	4.855	32.455	73.258
	Measurement-4	6.666	31.780	80.339
	Measurement-5	4.330	32.634	67.094
	Measurement-6	3.174	30.472	56.361
	Average	4.956	32.086	73.399
	% RSD	23.90	4.13	13.85
Intermediate Precision	Measurement-1	5.559	35.841	82.998
	Measurement-2	5.140	30.254	80.659
	Measurement-3	5.452	32.452	73.446
	Measurement-4	5.620	33.450	80.149
	Measurement-5	4.253	30.125	70.698
	Measurement-6	4.510	30.145	72.000
	Average	5.089	32.045	76.658
	% RSD	11.36	7.26	6.80
Cumulative Average		5.022	32.065	75.029
Cumulative % RSD		17.75	5.63	10.51

3.2.2 Robustness

The robustness of an analytical procedure is a measure of its capacity to remain unaffected by small, but deliberate variations in method parameters and provides an indication of its reliability during normal usage.

Robustness -1 (Change in stirrer speed to 1800 rpm)

The particle size of three replicates as per the method of analysis, only change the stirrer speed to 1800 rpm and recorded particle Size for d (0.1), d (0.5) & d (0.9) and similarly, calculated cumulative average and cumulative percent relative standard deviation for particle size at d (10), d (50) & d(90) of nine measurements were within limit. The results are shown in Table No.2

Table no. 2

Parameter	Measurement No.	d (10)	d (50)	d (90)
Robustness-1	Measurement-1	4.123	35.466	78.956
	Measurement-2	5.100	31.23	80.479
	Measurement-3	4.698	33.584	75.476
	Average	4.640	33.427	78.304
	% RSD	23.90	4.13	13.85
	Cumulative Average	4.850	32.533	75.534
	Cumulative % RSD	20.22	5.02	11.53

Robustness-2 (Change in stirrer speed to 2200 rpm)

The particle size of three replicates as per the method of analysis, only change the stirrer speed to 2200 rpm and recorded the particle Size for d(0.1), d(0.5) & d(0.9) and similarly, calculated cumulative average and cumulative percent relative standard deviation for particle size at d(10), d(50) & d(90) of nine measurements i.e. six of precision and three of Robustness-2 were within limit. The results are shown in Table No.3

Table no. 3

Parameter	Measurement No.	d (10)	d (50)	d (90)
Robustness-2	Measurement-1	4.181	35.739	78.925
	Measurement-2	4.975	32.46	71.523
	Measurement-3	5.231	31.485	74.551
	Average	4.796	33.227	75.000
	% RSD	0.547	2.229	3.721
	Cumulative Average	4.902	32.467	73.933
	Cumulative % RSD	19.97	5.03	11.21

Robustness-3 (Change the obscuration range to 10 – 20%)

The particle size of three replicates as per the method of analysis, only change the obscuration range to 10 – 20% and recorded the particle size for d(0.1), d(0.5) & d(0.9) and Similarly, calculated cumulative average and cumulative percent relative standard deviation for particle size at d(10), d(50) & d(90) of nine measurements i.e. six of precision and three of Robustness-3 were within limit. The results are shown in Table No.4

Table no. 4

Parameter	Measurement No.	d (10)	d (50)	d (90)
Robustness-3	Measurement-1	5.416	36.125	80.245
	Measurement-2	5.001	32.416	75.245
	Measurement-3	5.463	35.418	78.756
	Average	5.293	34.653	78.082
	% RSD	0.254	1.969	2.567
	Cumulative Average	5.068	32.942	74.960

	Cumulative % RSD	4.90	5.85	11.30

Robustness-4 (Change the obscuration range to 20 – 30%)

The particle size of three replicates as per the method of analysis, only changed the obscuration range to 20 – 30 % and recorded the particle size for d(0.1), d(0.5) & d(0.9) and similarly, calculated cumulative average and cumulative percent relative standard deviation for particle size at d(10), d(50) & d(90) of nine measurements i.e. six of precision and three of Robustness-4 were within limit. The results are shown in Table No.5

Table no. 5

Parameter	Measurement No.	d (10)	d (50)	d (90)
Robustness-4	Measurement-1	5.325	35.219	71.180
	Measurement-2	5.418	36.147	82.875
	Measurement-3	4.995	36.789	83.880
	Average	5.293	34.653	78.082
	% RSD	0.254	1.969	2.567
	Cumulative Average	5.052	33.408	75.370
	Cumulative % RSD	18.88	6.82	12.29

Robustness - 5 (Change in sample measurement time to 9 seconds from 10 seconds)

The particle size of three replicates as per the method of analysis, only changed the sample measurement time to 9 seconds and recorded the particle size for d(0.1), d(0.5) & d(0.9) and similarly, calculated cumulative average and cumulative percent relative standard deviation for particle size at d(10), d(50) & d(90) of nine measurements i.e. six of precision and three of Robustness-5 were within limit. The results are shown in Table No.6

Table no. 6

Parameter	Measurement No.	d (10)	d (50)	d (90)
Robustness-5	Measurement-1	5.102	36.859	80.589
	Measurement-2	4.996	36.147	68.258
	Measurement-3	4.512	35.201	72.159
	Average	4.870	36.069	73.669
	% RSD	0.315	0.832	6.303
	Cumulative Average	4.927	33.414	73.489
	Cumulative % RSD	19.29	6.85	11.75

Robustness - 6 (Change in sample measurement time to 11 seconds from 10 seconds)

The particle size of three replicates as per the method of analysis, only changed the sample measurement time to 11 seconds and recorded the particle size for d (0.1), d (0.5) & d(0.9) and similarly, calculated cumulative average and cumulative percent relative standard

deviation for particle size at d(10), d(50) & d(90) of nine measurements i.e. six of precision and three of Robustness-6 were within limit. The results are shown in Table No.7

Table no. 7

Parameter	Measurement No.	d (10)	d (50)	d (90)
Robustness-6	Measurement-1	4.985	34.259	80.487
	Measurement-2	4.854	32.458	75.417
	Measurement-3	4.231	30.124	77.158
	Average	4.690	32.280	77.687
	% RSD	0.403	2.073	2.576
	Cumulative Average	4.867	32.151	74.829
	Cumulative % RSD	19.87	4.59	11.25

The result was getting from method validation parameters Precision, Intermediate Precision, and Robustness, The % RSD d(10) particle size values were found not more than 30 due to the particle size was less than 10,d(90) particle size values were found not more than 15, d(50) particle size values were found not more than 10.

4.0 CONCLUSION

The method of determination of particle size distribution for Lumefantrine has been successfully developed and validated using the Laser diffraction technique. Wet dispersion was explored during development trials. The wet dispersant method by using water as a dispersant medium was frozen for the determination of particle size distribution of Lumefantrine.

In method validation, method were found précised with % RSD of 23.90% for d(0.1), 4.13% for d(0.5) and 13.85% for d(0.9). In intermediate precision % RSD obtained were 11.36% for d(0.1), 7.26% for d(0.5) and 6.80% for d(0.9). Also, Cumulative % RSD obtained were 17.75% for d (0.1), 5.63% for d (0.5) and 10.51% for d (0.9).

This method is considered rugged. All the particle size data of development and validation have been compiled and found to be satisfactory. Hence, the method developed for the particle size method can be suitably used for the analysis of Lumefantrine active pharmaceutical ingredients.

ACKNOWLEDGMENT

the authors wish to extend their gratitude to Indoco Remedies Ltd. For providing all kinds of support. The author wishes to thank Indoco Remedies ltd and all our colleagues and Mr.

Shivaji Folane for his valuable support, who provided technical assistance during the journey of the research paper.

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