

Development and Validation of New Analytical Method for the Determination of Particle Size Distribution in Glimepiride Using Laser Based Particle Size Analyzer

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Abstract: Particle size is a key factor for modern drug quality since it affects the bioavailability and dissolution profile of the drug product. Study for Particle size is helpful to optimize drug product development process and improve the quality of drugs. In Order to determine the particle size of Glimepiride a novel and accurate Particle size determination method has been developed for the determination of particle size distribution of Glimepiride was described in this paper. This method has shown good reproducible results. By using water as dispersant wet method is developed and validated as per International conference on Harmonization guidelines (Q2 (R1)) and found out robust and reproducible with % RSD of d (10), d (50) and d (90) values found within acceptance limit ranges from 6.05% to 21.84% for d(0.1), 3.04% to 9.87% for d(0.5) and 4.69% to 14.32% for d(0.9) in validation. The described method is accurate and validated and successfully applied for the determination of particle size distribution of Glimepiride. Particle size method is discussed in detail to ensure in-depth understanding of particle size distribution and particle size method performance during lifetime of the product.

Keywords: Glimepiride, Method development, Method validation, Particle size analyzer.

1. Introduction

Glimepiride is a white to yellowish-white, odorless powder and is practically insoluble in water. Glimepiride acts as an insulin secretagogue and it lowers blood sugar by stimulating the release of insulin by pancreatic beta cells and by inducing increased activity of intracellular insulin receptors [1]. Glimepiride chemically, is 3-ethyl-4-methyl-N-[2-[4-(4-methylcyclohexyl)carbamoylsulfamoyl] phenyl] ethyl]-2-oxo-5H-pyrrole-1-carboxamide is a third generation sulfonylurea derivative which is commonly used in the treatment of non-insulin dependent Type 2 diabetes mellitus [2-5]. Glimepiride, marked under the trade name Amaryl, is the first line medication for the treatment of type-2 diabetes mellitus [6-8].

Relative bioavailability, extended-released along with bioequivalence and immediate released is related to particle size of Glimepiride [9-12]. Literature survey done for Particle size distribution method for Glimepiride and found that particle size determination method is not available. Therefore, study was carried out to develop a method to determine particle size distribution of Glimepiride by Particle size analyzer and further validation of the method, was carried out.

2. Materials and Reagent

2.1. Reagents

Triton x-100, water and Glimepiride was obtained from Indoco Remedies Ltd, Navi Mumbai, India.

2.2. Instrumentation

Particle size analyzer system of make Malvern and model is 2000 consists of Dry Scirocco 2000 and wet Hydro2000S accessories.

3. Results and Discussion

3.1. Analytical Method Development

The main goal was to develop method to obtain the most stable, reproducible, reliable method. Various dispersant were tried for the Glimepiride on the basis of solubility. Water is found well suitable dispersant to develop method for determination of particle size distribution of Glimepiride. Various trial were taken during method development as mention below, Glimepiride solubility within a suitable solvent system a critical role in particle size wet method development since sample preparation is play vital role. Make Malvern Mastersizer, Model Mastersizer 2000, Dispersion Unit Scirocco 2000, Method parameters are kept as Particle Refractive index is 1.520, Absorption is 0.1, Analysis Model General purpose, Obscuration range is 1% to 6%, Dispersive Air pressure is 2.0 bar, Vibration feed rate is 40%, Sensitivity is Normal, Sample measuring time 5 seconds, Background measuring time 5 seconds, sample preparation is Transferred about 1 to 2 g of sample into the sample tray with the help of a cleaned spatula and carried out the analysis The obscuration values are well within the limit and also weighted residual is less than 1%. Hence, proceeded for next trial by changing the feed rate 45% to check the effect on particle size. Various trials were taken by changing instrumental parameters. The obtained results of d(10), d(50) and d(90) values are not reproducible and % RSD is also not well within general criteria of USP, General Chapter <429>. Hence next development was carried out by wet analysis. Method parameters for wet analysis is Equipment Malvern Mastersizer, Model Mastersizer 2000, Sample handling unit is Wet Dispersion Unit, Sample model is Hydro 2000S, Dispersant name is Water, Dispersant refractive index is 1.330, Sample refractive index is 1.520, Sample absorption is 0.1, Sample measurement time is 10 second, Measurement Snaps is 10,000. Background Measurement time is 10 second, Background Snaps 10,000, Obscuration range is 10-30%, Stirrer speed is 2000 rpm, No. of measurement cycle 03, sample preparation is Weighed 200.26 mg of sample and transferred in beaker added 1-2 drops of Triton x-100 and few drops of dispersant and make a paste by using glass rod, then added 20 mL of dispersant. Sonicate externally for 40 seconds to form homogeneous solution. Sample solution was added in the dispersion unit when "Add sample under Obscuration" message was shown by the instrument software and performed the analysis.

All method parameters were kept as per above only changed in sonication time 50 Sec. and performed the analysis. The obscuration is well within limit it is proved that there is no any effect of sonication time on particle size, Hence, preceded for next trial by changing stirrer speed check the effect on particle size. The obscuration values are well within the limit, from the obtained results there is negligible effect on the particle size by decreased in stirrer speed. Hence, Malvern Mastersizer, Model Mastersizer 2000, Sample handling unit is Wet Dispersion Unit, Sample model is Hydro 2000S, Dispersant name is Water, Dispersant refractive index is 1.330, Sample refractive index is 1.520, Sample absorption is 0.1, Sample measurement time is 10 second, and Measurement Snaps is 10,000. Background Measurement time is 10 second, Background Snaps 10,000, Obscuration range is 10-30%, Stirrer speed is 1800 rpm, No. of measurement cycle 03.

Performed analysis repeatability with weight 200.68, 200.96 mg and 200.31 mg to check consistency. The obtained results of d(10), d(50), and d(90) values of analysis in twice are close to each other, weighted residue is less than 1% and obscuration is found satisfactory. To check the reproducibility of method three replicate of sample was analyzed and results were found reproducible & percentage Relative standard deviation of d(10), d(50), and d(90) is respectively 4.27%, 9.83% and 14.45 %.

3.2. Method Validation

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

4. Method Validation Parameters

4.1. Method Precision

Procedure: Determined the particle size of six precision samples as per above method and recorded the particle size for d(0.1), d(0.5) and d(0.9) in **Table 1**.

Table 1.
Method precision.

Sample ID	Particle size (μm)		
	d(0.1)	d(0.5)	d(0.9)
Precision-1	2.553	15.654	64.835
Precision-2	2.697	17.513	76.598
Precision-3	2.77	18.122	76.865
Precision-4	2.578	16.981	63.762
Precision-5	2.897	17.489	83.82
Precision-6	2.766	17.871	74.388
Average	2.71	17.272	73.378
% RSD	4.78	5.11	10.52

Acceptance criteria: The % RSD d(10), d(90) particle size values should not be more than 15, d(50) particle size values should not be more than 10. If the particle size is below 10 μm then the % RSD of d(10), d(50), and d(90) will be doubled.

4.2. Intermediate Precision

Procedure: Determined the particle size of six Intermediate precision samples as per above method and recorded the particle size for d(0.1), d(0.5) & d(0.9) particles in **Table 2** and similarly, calculated cumulative average and cumulative percent relative standard deviation for particle size at d(10), d(50) & d(90) of twelve measurements i.e. six of precision and six of Intermediate precision.

Table 2.
Intermediate precision.

Sample ID	Particle size (μm)		
	d(0.1)	d(0.5)	d(0.9)
Intermediate precision-1	2.725	17.744	79.323
Intermediate precision-2	2.624	17.172	75.362
Intermediate precision-3	2.486	17.48	70.604
Intermediate precision-4	2.75	18.339	80.652
Intermediate precision-5	2.784	18.686	82.782
Intermediate precision-6	2.795	18.057	74.775
Average	2.694	17.913	77.25
%RSD	4.41	3.12	5.8
Precision-1	2.553	15.654	64.835
Precision-2	2.697	17.513	76.598
Precision-3	2.77	18.122	76.865
Precision-4	2.578	16.981	63.762
Precision-5	2.897	17.489	83.82
Precision-6	2.766	17.871	74.388
Cumulative average	2.702	17.592	75.314
Cumulative % RSD	4.4	4.43	8.43

Acceptance criteria: The % RSD d(10), d(90) particle size values should not be more than 15, d(50) particle size values should not be more than 10. If the particle size is below 10 μm then the % RSD of d(10), d(50), and d(90) will be doubled.

5. Robustness

5.1. Robustness-1 (Change in Stirrer Speed to 1800 rpm)

Procedure: Determined the particle size of three replicates as per 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) in **Table 3** 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-1.

Table 3.
Robustness-1 (Change in stirrer speed to 1800 rpm).

Sample ID	Particle size (μm)		
	d(0.1)	d(0.5)	d(0.9)
Robustness-1(1)	2.783	18.529	80.054
Robustness-1(2)	2.925	19.554	78.597
Robustness-1(3)	2.901	19.423	80.885
Average	2.87	19.169	79.845
% RSD	2.65	2.91	1.45
Precision-1	2.553	15.654	64.835
Precision-2	2.697	17.513	76.598
Precision-3	2.77	18.122	76.865
Precision-4	2.578	16.981	63.762
Precision-5	2.897	17.489	83.82
Precision-6	2.766	17.871	74.388
Cumulative average	2.763	17.904	75.534
Cumulative % RSD	4.9	6.76	9.18

Acceptance criteria: The % RSD d(10), d(90) particle size values should not be more than 15, d(50) particle size values should not be more than 10. If the particle size is below 10 μm then the % RSD of d(10), d(50), and d(90) will be doubled.

5.2. Robustness-2 (Change in Stirrer Speed to 2200 rpm)

Procedure: Determined the particle size of three replicates as per 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) in **Table 4** 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.

Table 4.
Robustness-2 (Change in stirrer speed to 2200 rpm).

Sample ID	Particle size (μm)		
	d(0.1)	d(0.5)	d(0.9)
Robustness-2(1)	2.81	18.692	77.187
Robustness-2(2)	3.23	17.95	89.245
Robustness-2(3)	3.122	17.852	89.001
Average	3.054	18.165	85.144
% RSD	7.14	2.53	8.09
Precision-1	2.553	15.654	64.835
Precision-2	2.697	17.513	76.598
Precision -3	2.77	18.122	76.865
Precision -4	2.578	16.981	63.762
Precision -5	2.897	17.489	83.82
Precision -6	2.766	17.871	74.388
Cumulative average	2.825	17.569	77.3
Cumulative % RSD	8.07	4.89	11.84

Acceptance criteria: The % RSD d(10), d(90) particle size values should not be more than 15, d(50) particle size values should not be more than 10. If the particle size is below 10 μm then the % RSD of d(10), d(50), and d(90) will be doubled.

5.3. Robustness-3 (Change in Obscuration Range to 10-20%)

Procedure: Determined the particle size of three replicates as per 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) in **Table 5** 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.

Table 5.
Robustness-3 (Change in Obscuration range to 10-20%).

Sample ID	Particle size (μm)		
	d(0.1)	d(0.5)	d(0.9)
Robustness-3(1)	2.838	19.476	85.459
Robustness-3(2)	3.179	18.953	95.103
Robustness-3(3)	2.767	18.475	79.326
Average	2.928	18.968	86.629
% RSD	7.52	2.64	9.18
Precision -1	2.553	15.654	64.835
Precision -2	2.697	17.513	76.598
Precision -3	2.77	18.122	76.865
Precision -4	2.578	16.981	63.762
Precision -5	2.897	17.489	83.82
Precision -6	2.766	17.871	74.388
Cumulative average	2.783	17.837	77.795
Cumulative % RSD	6.67	6.31	12.66

Acceptance criteria: The % RSD d(10), d(90) particle size values should not be more than 15, d(50) particle size values should not be more than 10. If the particle size is below 10 μm then the % RSD of d(10), d(50), and d(90) will be doubled.

5.4. Robustness-4 (Change in Obscuration Range to 20-30%)

Procedure: Determined the particle size of three replicates as per 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) in **Table 6** 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.

Table 6.
Robustness-4 (Change in Obscuration range to 20-30%).

Sample ID	Particle size (μm)		
	d(0.1)	d(0.5)	d(0.9)
Robustness-4(1)	2.304	17.958	79.025
Robustness-4(2)	2.778	18.596	82.875
Robustness-4(3)	2.869	19.828	83.88
Average	2.65	18.794	81.927
% RSD	11.45	5.06	3.13
Precision -1	2.553	15.654	64.835
Precision -2	2.697	17.513	76.598
Precision -3	2.77	18.122	76.865
Precision -4	2.578	16.981	63.762
Precision -5	2.897	17.489	83.82
Precision -6	2.766	17.871	74.388
Cumulative average	2.69	17.779	76.228
Cumulative % RSD	6.89	6.39	9.92

Acceptance criteria: The % RSD d(10), d(90) particle size values should not be more than 15, d(50) particle size values should not be more than 10. If the particle size is below 10 μm then the % RSD of d(10), d(50), and d(90) will be doubled.

5.5. Robustness - 5 (Change in Sample Measurement Time to 9 Seconds from 10 Seconds)

Procedure: Determined the particle size of three replicates as per method of analysis, only changed the sample measurement time to 3 seconds and recorded the particle size for d(0.1), d(0.5) & d(0.9) in **Table 7** 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.

Table 7.
Robustness - 5 (Change in sample measurement time to 9 seconds from 10 seconds).

Sample ID	Particle size (μm)		
	d(0.1)	d(0.5)	d(0.9)
Robustness-5(1)	2.801	19.021	78.032
Robustness-5(2)	2.837	18.746	76.702
Robustness-5(3)	2.738	18.462	77.897
Average	2.792	18.743	77.544
% RSD	1.79	1.49	0.94
Precision-1	2.553	15.654	64.835
Precision-2	2.697	17.513	76.598
Precision-3	2.77	18.122	76.865
Precision-4	2.578	16.981	63.762
Precision-5	2.897	17.489	83.82
Precision-6	2.766	17.871	74.388
Cumulative average	2.737	17.762	74.767
Cumulative % RSD	4.13	5.76	8.64

Acceptance criteria: The % RSD d(10), d(90) particle size values should not be more than 15, d(50) particle size values should not be more than 10. If the particle size is below $10\ \mu\text{m}$ then the % RSD of d(10), d(50), and d(90) will be doubled.

5.6. Robustness - 6 (Change In Sample Measurement Time to 11 Seconds from 10 Seconds)

Procedure: Determined the particle size of three replicates as per method of analysis, only changed the sample measurement time to 7 seconds and recorded the particle size for d(0.1), d(0.5) & d(0.9) in **Table 8** 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.

Acceptance criteria: The % RSD d(10), d(90) particle size values should not be more than 15, d(50) particle size values should not be more than 10. If the particle size is below $10\ \mu\text{m}$ then the % RSD of d(10), d(50), and d(90) will be doubled.

6. Conclusion

Method for determination of particle size distribution of Glimpiride was developed and validated using Laser diffraction technique. Dry dispersion technique was assessed and found that dry dispersion technique is not suitable for and wet dispersion was explored during development trials. Wet dispersant method frozen for determination of particle size distribution of Glimpiride. In method validation, method was found precised with % RSD of 10.59% for d(0.1), 8.57% for d(0.5) and 14.32% for d(0.9).

In intermediate precision % RSD obtained were 6.05% for d(0.1), 3.04% for d(0.5) and 5.95% for d(0.9). Also, Cumulative % RSD obtained were 8.39% for d (0.1), 6.71% for d (0.5) and 5.12.40% for d (0.9). Hence, the method considered as rugged. certain parameters were modified within the allowed range and the results obtained were within the acceptance criteria and % RSD ranges from 6.22% to 21.84% for d(0.1), 3.47% to 9.87% for d(0.5) and 4-.69% to 12.85% for d(0.9). It proved method is rugged.

All the analytical data of development and validation has been compiled and found to be satisfactory. Hence, method developed for the particle size method can be suitably used for analysis of Glimpiride active pharmaceutical ingredient.

Table 8.
Robustness - 6 (Change in sample measurement time to 11 seconds from 10 seconds).

Sample no.	Particle size (μm)		
	d(0.1)	d(0.5)	d(0.9)
Robustness-6(1)	2.644	16.327	68.769
Robustness-6(2)	2.638	16.396	65.908
Robustness-6(3)	2.591	16.443	73.409
Average	2.624	16.389	69.362
% RSD	1.11	0.36	5.46
Precision-1	2.553	15.654	64.835
Precision-2	2.697	17.513	76.598
Precision-3	2.77	18.122	76.865
Precision-4	2.578	16.981	63.762
Precision-5	2.897	17.489	83.82
Precision-6	2.766	17.871	74.388
Cumulative average	2.682	16.977	72.039
Cumulative % RSD	4.18	4.86	9.3

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