

## Original Research Article

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

#### ABSTRACT

In this paper described rugged and precise particle size determination method has been developed and validated for the determination of particle size distribution of Ciprofloxacin Hydrochloride by dry method using Malvern Mastersizer 2000.

The Method of particle size distribution of Ciprofloxacin Hydrochloride was precisely developed and validated successfully. By using parameters like Precision, Intermediate precision, and Robustness the method was validated. All the particle size data has been compiled and found to be satisfactory, Hence the method is suitably used for the analysis for Particle size analyzer of Ciprofloxacin Hydrochloride active pharmaceutical ingredients.

*Keywords: [Ciprofloxacin Hydrochloride, Method Validation and Particle size analyzer (PSA)].*

#### 1. INTRODUCTION

Ciprofloxacin Hydrochloride is used to treat a variety of bacterial infections. [1] Ciprofloxacin belongs to a class of drugs called quinolone antibiotics. [2] It works by stopping the growth of bacteria. This antibiotic is used to treats bacterial infections. [3]

Particle size reduction is an integral part and it is direct remedy to increasing the exposure of poorly soluble oral drugs by increasing surface area and thereby improving the dissolution rate. [4] Particle size analysis has become an indirect means for routine surface area measurement. [5]Ciprofloxacin Hydrochloride 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 products, it is important to have an accurate method for the analysis of the Particle size distribution of Ciprofloxacin Hydrochloride. Therefore the study was carried out to establish a method to determine the particle size distribution of Ciprofloxacin Hydrochloride by particle size analyzer.

A study for Particle size is very critical to optimize the drug product development process and it play very important role in the quality of drugs as well as bioavailability of the drug product.[6] During the survey, it was observed that there is no such studies was done on this molecule for Particle Size determination. To determine the quality of these important drug products, it is important to have a precise method for the analysis of the Particle size distribution of Ciprofloxacin Hydrochloride Therefore the study was carried out to establish a method to determine the particle size distribution of Ciprofloxacin Hydrochloride by particle size analyzer.

## 2. MATERIAL AND METHODS

### Instrumentation

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

•Instrument General Parameter,

Equipment - Malvern Mastersizer, Model- Mastersizer 2000 (which uses 52 detectors array), Sample handling unit- Dry Dispersion Unit, Sample model- Scirocco 2000, Dispersant name- Air,

## RESULT AND DISCUSSION

### DEVALOPMENT:

Several physical and chemical properties of ciprofloxacin benzoate were obtained from the literature. An analytical particle size determination method was developed to select optical parameters of particle size conditions, including particle RI, Dispersant RI, particle absorption and sample preparation procedure. For this purpose, a series of trials were performed by varying the optical parameters in order to achieve the residue below the 1% which indicate that optical parameters are correct in nature and further results are reproducible and consistent in nature. During method development Dry mode and optimized optical are as parameters dispersant RI 1. Sample refractive 1.5, Feed rate- 50 %, sample absorption 0.0, Obscuration range- 0.5-6.0%, Air, Dispersant refractive index- 1.0, Air pressure- 3.0 Bar, sample measurement time 12 second and sample measurement snap 12000, background measurement time 12 second and background measurement snap are 1200 are suitable along with was optimized as the best particle measurement conditions for the entire study .

### 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.

### METHOD PRECISION & INTERMEDIATE PRECISION

% RSD as well as cumulative % RSD of Ciprofloxacin Hydrochloride during the study of the precision and intermediate precision was mentioned in the Table No.1, Table No.2 and Table No.3 respectively.[7]

### METHOD PRECISION:

TABLE NO.1: METHOD PRECISION

Sample ID	Percentage below (%)				Particle size (µm)
	5 µm	10 µm	15 µm	d(0.95)	
Precision-1	45.89	84.19	96.28	14.06	
Precision-2	44.81	82.78	94.81	15.17	
Precision-3	44.47	82.49	94.81	15.16	
Precision-4	43.86	82.10	94.49	15.43	
Precision-5	44.35	82.24	94.22	15.73	
Precision-6	44.15	82.06	94.17	15.75	

Average	44.59	82.64	94.80	15.22
%RSD	1.60	0.97	0.82	4.09

TABLE NO.2: INTERMEDIATE PRECISION

Sample ID	Percentage below (%)			Particle size (µm)
	5 µm	10 µm	15 µm	d(0.95)
Intermediate Precision-1	42.68	81.49	94.58	15.33
Intermediate Precision-2	42.87	81.56	94.47	15.43
Intermediate Precision-3	42.99	81.83	95.05	14.96
Intermediate Precision-4	44.31	83.21	96.11	14.24
Intermediate Precision-5	42.89	81.29	94.09	15.77
Intermediate Precision-6	44.47	82.62	94.68	15.28
Average	43.37	82.00	94.83	15.17
%RSD	1.84	0.92	0.74	3.46

TABLE NO.3: CUMULATIVE % RSD OF METHOD PRECISION AND INTERMEDIATE PRECISION

Sample ID	Percentage below (%)			Particle size (µm)
	5 µm	10 µm	15 µm	d(0.95)
Precision-1	45.89	84.19	96.28	14.06
Precision-2	44.81	82.78	94.81	15.17
Precision-3	44.47	82.49	94.81	15.16
Precision-4	43.86	82.10	94.49	15.43

Precision-5	44.35	82.24	94.22	15.73
Precision-6	44.15	82.06	94.17	15.75
Intermediate Precision-1	42.68	81.49	94.58	15.33
Intermediate Precision-2	42.87	81.56	94.47	15.43
Intermediate Precision-3	42.99	81.83	95.05	14.96
Intermediate Precision-4	44.31	83.21	96.11	14.24
Intermediate Precision-5	42.89	81.29	94.09	15.77
Intermediate Precision-6	44.47	82.62	94.68	15.28
Cumulative Average	43.98	82.32	94.81	15.19
%RSD	2.19	0.99	0.74	3.62

## ROBUSTNESS

Robustness is the measure of variation in end results by changing routine analytical parameters. In order to establish the robustness and provides an indication of its reliability during normal usage.

### ROBUSTNESS – 1:

The Robustness-1 was performed by changing the Feed rate to 45% from 50% and the results of individual % RSD as well as cumulative % RSD is mentioned in Table No.4 & 5

TABLE NO.4: ROBUSTNESS -1

Sample ID	Percentage below (%)			Particle size (µm)
	5 µm	10 µm	15 µm	
Robustness-1(1)	44.48	83.51	96.13	d(0.95) 14.18
Robustness-1(2)	42.24	80.49	93.25	16.64
Robustness-1(3)	41.01	78.87	91.97	18.02
Average	44.59	82.64	94.80	15.22
%RSD	1.60	0.97	0.82	4.09

TABLE NO.5: CUMULATIVE % RSD OF METHOD PRECISION AND ROBUSTNESS-1

Sample ID	Percentage below (%)			Particle size ( $\mu\text{m}$ )
	5 $\mu\text{m}$	10 $\mu\text{m}$	15 $\mu\text{m}$	d(0.95)
Precision-1	45.89	84.19	96.28	14.06
Precision-2	44.81	82.78	94.81	15.17
Precision-3	44.47	82.49	94.81	15.16
Precision-4	43.86	82.10	94.49	15.43
Precision-5	44.35	82.24	94.22	15.73
Precision-6	44.15	82.06	94.17	15.75
Robustness-1(1)	44.48	83.51	96.13	14.18
Robustness-1(2)	42.24	80.49	93.25	16.64
Robustness-1(3)	41.01	78.87	91.97	18.02
Cumulative Average	43.92	82.08	94.46	15.57
%RSD	3.30	1.93	1.41	7.79

#### ROBUSTNESS – 2:

The Robustness-2 was performed by changing the Feed rate to 55% from 50% and the results of individual % RSD as well as cumulative % RSD is mentioned in Table No.6 & 7

TABLE NO.6: ROBUSTNESS-2

Sample ID	Percentage below (%)			Particle size ( $\mu\text{m}$ )
	5 $\mu\text{m}$	10 $\mu\text{m}$	15 $\mu\text{m}$	d(0.95)
Robustness-2(1)	42.83	80.82	93.71	16.08

Robustness-2(2)	41.66	80.13	93.42	16.35
Robustness-2(3)	41.19	79.52	92.78	17.02
Average	41.89	80.16	93.30	16.48
%RSD	2.02	0.81	0.51	2.94

TABLE NO.7: CUMULATIVE % RSD OF METHOD PRECISION AND ROBUSTNESS-2

Sample ID	Percentage below (%)			Particle size ( $\mu\text{m}$ )
	5 $\mu\text{m}$	10 $\mu\text{m}$	15 $\mu\text{m}$	d(0.95)
Precision-1	45.89	84.19	96.28	14.06
Precision-2	44.81	82.78	94.81	15.17
Precision-3	44.47	82.49	94.81	15.16
Precision-4	43.86	82.10	94.49	15.43
Precision-5	44.35	82.24	94.22	15.73
Precision-6	44.15	82.06	94.17	15.75
Robustness-2(1)	42.83	80.82	93.71	16.08
Robustness-2(2)	41.66	80.13	93.42	16.35
Robustness-2(3)	41.19	79.52	92.78	17.02
Cumulative Average	43.69	81.81	94.30	15.64
%RSD	3.48	1.75	1.06	5.36

ROBUSTNESS – 3:

The Robustness-3 was performed by changing the Air Pressure 2.7 bar from 3 bar and the results of individual % RSD as well as cumulative % RSD is mentioned in Table No.8 & 9

TABLE NO.8: ROBUSTNESS-3

Sample ID	Percentage below (%)			Particle size ( $\mu\text{m}$ )
	5 $\mu\text{m}$	10 $\mu\text{m}$	15 $\mu\text{m}$	d(0.95)
Robustness-3(1)	39.07	77.31	91.20	18.87
Robustness-3(2)	41.61	81.27	95.07	14.95

Robustness-3(3)	39.24	78.04	92.35	17.13
Average	39.97	78.87	92.87	16.98
%RSD	3.55	2.67	2.14	11.56

TABLE NO.9: CUMULATIVE % RSD OF METHOD PRECISION AND ROBUSTNESS-3

Sample ID	Percentage below (%)			Particle size ( $\mu\text{m}$ )
	5 $\mu\text{m}$	10 $\mu\text{m}$	15 $\mu\text{m}$	d(0.95)
Precision-1	45.89	84.19	96.28	14.06
Precision-2	44.81	82.78	94.81	15.17
Precision-3	44.47	82.49	94.81	15.16
Precision-4	43.86	82.10	94.49	15.43
Precision-5	44.35	82.24	94.22	15.73
Precision-6	44.15	82.06	94.17	15.75
Robustness-3(1)	39.07	77.31	91.20	18.87
Robustness-3(2)	41.61	81.27	95.07	14.95
Robustness-3(3)	39.24	78.04	92.35	17.13
Cumulative Average	43.05	81.39	94.16	15.81
%RSD	5.76	2.77	1.61	8.92

#### ROBUSTNESS- 4:

The Robustness-4 was performed by changing the Air Pressure 3.3 bar from 3 bar and the results of individual % RSD as well as cumulative % RSD is mentioned in Table No.10 & 11

TABLE NO.10: ROBUSTNESS-4

Sample ID	Percentage below (%)			Particle size ( $\mu\text{m}$ )
	5 $\mu\text{m}$	10 $\mu\text{m}$	15 $\mu\text{m}$	d(0.95)
Robustness-4(1)	43.80	82.70	95.68	14.51
Robustness-4(2)	43.08	81.10	93.81	16.05
Robustness-4(3)	43.40	81.23	93.62	16.30
Average	43.43	81.68	94.37	15.62
%RSD	0.83	1.09	1.21	6.21

TABLE NO.11: CUMULATIVE % RSD OF METHOD PRECISION AND ROBUSTNESS-4

Sample ID	Percentage below (%)			Particle size ( $\mu\text{m}$ )
	5 $\mu\text{m}$	10 $\mu\text{m}$	15 $\mu\text{m}$	d(0.95)
Precision-1	45.89	84.19	96.28	14.06
Precision-2	44.81	82.78	94.81	15.17
Precision-3	44.47	82.49	94.81	15.16
Precision-4	43.86	82.10	94.49	15.43
Precision-5	44.35	82.24	94.22	15.73
Precision-6	44.15	82.06	94.17	15.75
Robustness-4(1)	43.80	82.70	95.68	14.51
Robustness-4(2)	43.08	81.10	93.81	16.05
Robustness-4(3)	43.40	81.23	93.62	16.30
Cumulative Average	44.20	82.32	94.65	15.35
%RSD	1.88	1.11	0.91	4.69

## ROBUSTNESS- 5:

The Robustness-5 was performed by changing in the sample measurement time to 10 seconds from 12 seconds and the results of individual % RSD as well as cumulative % RSD is mentioned in Table No.12 & 13

TABLE NO.12: ROBUSTNESS - 5

Sample ID	Percentage below (%)			Particle size ( $\mu\text{m}$ )
	5 $\mu\text{m}$	10 $\mu\text{m}$	15 $\mu\text{m}$	d(0.95)
Robustness-5(1)	43.22	79.88	92.22	17.91
Robustness-5(2)	42.53	80.46	93.46	16.31
Robustness-5(3)	42.05	78.92	91.27	20.36
Average	42.60	79.75	92.32	18.19
%RSD	1.38	0.98	1.19	11.21

TABLE NO.13: CUMULATIVE % RSD OF METHOD PRECISION AND ROBUSTNESS-5

Sample ID	Percentage below (%)			Particle size ( $\mu\text{m}$ )
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	5 µm	10 µm	15 µm	d(0.95)
Precision-1	45.89	84.19	96.28	14.06
Precision-2	44.81	82.78	94.81	15.17
Precision-3	44.47	82.49	94.81	15.16
Precision-4	43.86	82.10	94.49	15.43
Precision-5	44.35	82.24	94.22	15.73
Precision-6	44.15	82.06	94.17	15.75
Robustness-5(1)	43.22	79.88	92.22	17.91
Robustness-5(2)	42.53	80.46	93.46	16.31
Robustness-5(3)	42.05	78.92	91.27	20.36
Cumulative Average	43.93	81.68	93.97	16.21
%RSD	2.69	1.99	1.58	11.54

#### ROBUSTNESS- 6:

The Robustness-5 was performed by changing in the sample measurement time to 14 seconds from 12 seconds and the results of individual % RSD as well as cumulative % RSD is mentioned in Table No.14 & 15

TABLE NO.14: ROBUSTNESS - 6

Sample ID	Percentage below (%)				Particle size (µm)
	5 µm	10 µm	15 µm	d(0.95)	
Robustness-6(1)	41.40	79.66	93.03	16.74	
Robustness-6(2)	42.39	81.24	94.66	15.25	
Robustness-6(3)	41.52	79.75	93.20	16.49	
Average	41.77	80.22	93.63	16.16	
%RSD	1.29	1.11	0.96	4.94	

TABLE NO.15: CUMULATIVE % RSD OF METHOD PRECISION AND ROBUSTNESS-6

Sample ID	Percentage below (%)				Particle size (µm)
	5 µm	10 µm	15 µm	d(0.95)	
Precision-1	45.89	84.19	96.28	14.06	
Precision-2	44.81	82.78	94.81	15.17	
Precision-3	44.47	82.49	94.81	15.16	

Precision-4	43.86	82.10	94.49	15.43
Precision-5	44.35	82.24	94.22	15.73
Precision-6	44.15	82.06	94.17	15.75
Robustness-6(1)	41.40	79.66	93.03	16.74
Robustness-6(2)	42.39	81.24	94.66	15.25
Robustness-6(3)	41.52	79.75	93.20	16.49
Cumulative Average	43.65	81.83	94.41	15.53
%RSD	3.53	1.76	1.02	5.09

#### 4. CONCLUSION

The method of determination of particle size distribution for Ciprofloxacin Hydrochloride has been successfully developed and validated using the Laser diffraction technique. Dry dispersion was explored during development trials of Ciprofloxacin Hydrochloride.

In method validation, method were found précised with % RSD 1.60%, 0.97%, 0.82 for percentage below 5µm, 10µm, 15µm and %RSD 4.09% for d (95). In intermediate precision % RSD obtained were 1.84%, 0.92%, 0.74 for percentage below 5µm, 10µm, 15µm and %RSD 3.46% for d (95). Also, Cumulative % RSD 2.19%, 0.99%, 0.74 for percentage below 5µm, 10µm, 15µm and %RSD 3.62% for d (95).

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 using dry dispersion can be suitably used for the analysis of Ciprofloxacin Hydrochloride active pharmaceutical ingredients.

#### COMPETING INTERESTS DISCLAIMER:

Authors have declared that they have no known competing financial interests OR non-financial interests OR personal relationships that could have appeared to influence the work reported in this paper.

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