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Development and Validation of Novel Analytical Method for the Determination of Particle Size Distribution in Ciprofloxacin Hydrochloride Using Laser-based Particle Size Analyzer

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Authors' contributions

This work was carried out in collaboration among all authors. Author SJ designed the study, performed the statistical analysis, wrote the protocol, and wrote the first draft of the manuscript. Authors CP, VP and SN managed the analyses of the study. Author AG managed the literature searches. All authors read and approved the final manuscript.

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ABSTRACT

This paper described a rugged and precise particle size determination method that has been developed and validated for the determination of particle size distribution of Ciprofloxacin Hydrochloride by a dry method using Malvern Mastersizer 2000.
The Method of the 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 of the Particle size analyzer of Ciprofloxacin Hydrochloride active pharmaceutical ingredients.

Keywords: Ciprofloxacin hydrochloride; method validation; Particle Size Analyzer (PSA).

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1. INTRODUCTION

Ciprofloxacin Hydrochloride is used to treat a variety of bacterial infections [1,2]. Ciprofloxacin belongs to a class of drugs called quinolone antibiotics [3]. It works by stopping the growth of bacteria. This antibiotic is used to treat bacterial infections [4,5].

Particle size reduction is an integral part and it is the direct remedy to increasing the exposure of poorly soluble oral drugs by increasing surface area and thereby improving the dissolution rate [6]. Particle size analysis has become an indirect means for routine surface area measurement [7,8]. 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 optimizing the drug product development process and it plays a very important role in the quality of drugs as well as the bioavailability of the drug product [9]. During the survey, it was observed that there is no such studies were 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 by using the dry dispersant technique and Ciprofloxacin Hydrochloride API will be employed for analysis to get results to conform the usability of the particle size determination of method. The current study is intended to determine the particle size of API Ciprofloxacin Hydrochloride crystal, which may perform better in pharmaceutical manufacturing processes and will result in better control of the manufacturing of drug products.

2. MATERIAL AND METHODS

2.1 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,

3. RESULT AND DISCUSSION

3.1 Development

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 a residue below the 1% which indicates 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 measurementseconds12 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.

3.2 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.

3.3 Method Precision and Intermediate Precision

% RSD, as well as cumulative % RSD of Ciprofloxacin Hydrochloride during the study of the precision and intermediate precision, was mentioned in Table 1, 2, and 3 respectively [10,11].

3.4 Method Precision

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 4 and 5.

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 6 and 7.

Robustness – 3:

The Robustness-3 was performed by changing the Air Pressure to 2.7 bar from 3 bar and the results of individual % RSD as well as cumulative % RSD is mentioned in Table 8 and 9.

Robustness- 4:

The Robustness-4 was performed by changing the Air Pressure to 3.3 bar from 3 bar and the results of individual % RSD as well as cumulative % RSD is mentioned in Table 10 and 11.

Robustness- 5:

The Robustness-5 was performed by changing 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 12 and 13.

Robustness- 6:

The Robustness-6 was performed by changing 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 14 and15.

Table 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 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 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

Table 4. Robustness -1

Sample ID	Percentage below (%)		Particle size (µm)	
	5 µm	10 µm	15 µm	d(0.95)
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
Average	44.59	82.64	94.80	15.22
%RSD	1.60	0.97	0.82	4.09

Table 5. Cumulative % RSD of Method Precision And Robustness-1

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-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

Table 6. Robustness-2

Sample ID	Percentage below (%)		Particle size (µm)	
	5 µm	10 µm	15 µm	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 7. Cumulative % RSD of method precision and robustness-2

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-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

Table 8. Robustness-3

Sample ID	Percentage below (%)			Particle size (µm)
	5 µm	10 µm	15 µm	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 9. Cumulative % RSD of method precision and robustness-3

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-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

Table 10. Robustness-4

Sample ID	Percentage below (%)			Particle size (µm)
	5 µm	10 µm	15 µm	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 11. Cumulative % RSD of method precision and robustness-4

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-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

Table 12. Robustness – 5

Sample ID	Percentage below (%)			Particle size (µm)
	5 µm	10 µm	15 µm	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 13. Cumulative % RSD of method precision and robustness-5

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-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

Table 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 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, methods were found précised with % RSD 1.60%, 0.97%, 0.82 for percentages 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.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

The 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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