ANALYTICAL METHOD DEVELOPMENT AND VALIDATION FOR THE DETERMINATION OF PARTICLE SIZE DISTRIBUTION IN COMBINED DOSAGE FORM (SULFAMETHOXAZOLE AND TRIMETHOPRIM ORAL SUSPENSION USP)

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ABSTRACT

Employing the Malvern Mastersizer 3000, a quick and robust particle size distribution method was developed and validated for determining the particle size of Sulfamethoxazole/Trimethoprim USP 200 mg/40 mg per 5 ml oral suspension. Particle size is a significant quality criterion for pharmaceutical products that are either solid dosage forms or liquids containing undissolved medicinal substances. In solid or suspension medicinal formulations, particle size can have a substantial effect on dissolving rates, bioavailability, and stability. This approach has produced good, reproducible results. Water is used as a dispersant to produce the wet technique. Validation was performed in accordance with the International Conference on Harmonisation requirements (Q2 (R1)) and found to be robust and reproducible, with % RSD values of d (0.1), d (0.9), and d (0.5) falling within acceptable limits. The described approach has been precisely developed, validated, and effectively implemented to determine the particle size distribution of. The particle size approach is presented in full to ensure a thorough understanding of particle size distribution, and it can be used to determine Sulfamethoxazole/Trimethoprim USP 200 mg/40 mg per 5 ml oral suspension particle size. The approach has been validated for precision, intermediate precision, and robustness.

INTRODUCTION

Over the last thirty years, trimethoprim and sulfamethoxazole have been an essential component in the treatment of a number of common infections. They have also shown especially effective for a number of specialised clinical situations.A commonly administered antibiotic with broad antibacterial action is trimethoprim-sulfamethoxazole.[1] The use of high dose trimethoprim-sulfamethoxazole has increased significantly due to the growing number of AIDS patients needing therapy for Pneumocystis cariniipneumonia. Tetrahydrofolic acid, the physiologically active form of folic acid and an essential cofactor in the production of thymidine, purines, and bacterial DNA, is inhibited by trimethoprim and sulfamethoxazole in bacteria.Asulfonamide medication called sulfamethoxazole blocks the formation of the intermediate dihydrofolic acid from its precursors. It is a structural analogue of para-aminobenzoic acid.

As a structural equivalent of the pteridine component of dihydrofolic acid,

trimethoprim inhibits dihydrofolatereductase and, as a result, the conversion of dihydrofolic acid into tetrahydrofolic acid in a competitive manner[2]. This two enzymes in one pathway are sequentially blocked, which has a bactericidal effect.All of the procedures that go into creating a formulation require an understanding of particle size and size characterization.[3] Particle size distribution (PSD) may significantly affect the therapeutic quality of products (dissolution rate, bioavailability, content homogeneity, etc.) in the pharmaceutical sector. The process of characterising a particle sizes in order to better comprehendand optimise its pharmacokinetic characteristics.[4-5]

A review of the literature on the particle size distribution method for oral suspensions of trimethoprim and sulfamethoxazole revealed that there is no known method for determining particle size.[6-10]Consequently, research was done to create a technique for using a particle size analyzer to measure the particle size distribution of trimethoprim and sulfamethoxazole oral suspension, and additional testing was done to validate the technique.This study presents a simple, robust, accurate, and precise method for determining the particle size distribution of an oral suspension containing trimethoprim and sulfamethoxazole in combination. The solvent system and widely accessible common instrument are used in the suggested PSD approach. The validation process followed the guidelines provided by the International Conference on Harmonisation (ICH).[11]

MATERIALS AND METHODS

Drugs and chemicals

Sulfamethoxazole/Trimethoprim USP 200mg/40 mg per 5 mloral suspension Active Pharmaceutical Ingredient, Milli-Q Water.

Instrumentation

The Malvern (2000) system, which was outfitted with Hydro accessories (2000S), was utilised for the development and validation of the particle size method. Data processing and evaluation were conducted using Mastersizer Software (Version 5.61).

Sample preparation

The sample shaken well for one minute.Transferred the sample directly into the sampling unit drop wise until the obscuration reaches in between 10-20%.

Instrument Parameter

Sample refractive index	:	1.641
Dispersant	:	
Water		
Dispersant R1	:	1.33
Absorption	:	0.1
Analysis model	:	
General purpose		
Sensitivity	:	
Normal		
Particle shape	:	
Irregular		
Measurement time seconds	:	12
Background time seconds	:	12
Obscuration 20%	:	10%-
RPM	:	2200
Measurement cycle	:	3

Particle Size Distribution Measurement Procedure

Pour the dispersant solution into the sampling equipment until it is full. Select

Configure accessory from the toolbar. Raise the stirrer/pump gradually until it reaches 2200 RPM by hand. Refill the sampling unit to the rim with dispersant solution once some of the unit's dispersant solution is displaced. The instrument was

set up in the wet analysis mode. Make sure that the sample unit is free of air bubbles. Started by measuring the background. Should the background laser intensity measurement be less than 50%, the sampling unit will restart the cleaning process. Using a transfer pipette, add sample dispersion to the sampling device until 10%–20% obscuration is reached. Results of average age were noted.

Cleaning procedure

Rinse the hydro 2000S (A) sampling unit with water. To avoid sample contamination after each measurement the sampling unit should be rinsed three to four times with dispersant before the following measurement is taken.

RESULTS AND DISCUSSION

Method Validation

Method precision

The precision of the particle size method was determined by transferring six individual sample preparations into the sampling unit and particle size distribution has been recorded **(Figure 1)**. The %RSD for particle size at D (0.1) and D (0.9) should be not more than 15%, and for D (0.5), it should be not more than 10%. **(Table 1).**

Table 1 Method Precision

S.No	D(0.1) µm	D(0.5) µm	D(0.9) µm
1	11.566	52.856	115.045
2	10.593	51.301	115.254
3	10.649	51.935	113.464
4	10.034	50.212	112.140
5	12.155	54.083	118.358
6	9.755	50.082	110.581
Average	10.792	51.745	114.140
%RSD	8	3	2

Intermediate precision

The precision of the particle size method was determined by transferring six individual sample preparations into the sampling unit by Analyst-2 on a different day, and the particle size distribution was recorded. The %RSD for particle size at D(0.1) and D(0.9) should be not more than 15%, and for D(0.5), it should be not more than 10%. **(Table 2)**

Table 2 Intermediate Precision

Sample No	Analyst-1			Analyst-2		
	D(0.1) µm	D(0.5) µm	D(0.9) µm	D(0.1) µm	D(0.5) µm	D(0.9) µm
1	11.566	52.856	115.045	12.369	55.054	118.738
2	10.593	51.301	115.254	10.560	54.137	117.225
3	10.649	51.935	113.464	9.797	47.907	106.954
4	10.034	50.212	112.140	12.013	54.102	117.395
5	12.155	54.083	118.358	12.046	53.519	115.257
6	9.755	50.082	110.581	10.532	51.471	110.862
Average	10.792	51.745	114.140	11.220	52.698	114.405

%RSD	8	3	2	10	5	4

Robustness

The robustness of the method is determined by varying instrument parameters such as stirring speed (±200 RPM and Obscuration) at 5% and 10%. PSD was recorded for the sample solution, and %RSD was calculated for D(0.1), D(0.5), and D(0.9). The %RSD for particle size at D(0.1) and D(0.9) should be not more than 15%, and for D(0.5), it should be not more than 10%. **(Table 3)**

Table 3 Robustness - Stirring speed

Measurement No	Stirring speed (RPM)	D(0.1) µm	D(0.5) µm	D(0.9) µm
1	2000	13.892	57.307	124.949
2		13.704	57.128	123.252
3		13.062	56.725	122.250
Average		13.553	57.053	123.574
%RSD		3	1	1
1	2400	11.381	52.563	114.982
2		11.792	52.085	112.994
3		11.137	51.417	111.634
Average		11.437	52.022	113.203
%RSD		3	1	1

Table 4 Robustness - Obscuration

Measurement No	Obscuration	D(0.1) µm	D(0.5) µm	D(0.9) µm
1	10%	12.776	55.499	122.774
2		13.912	56.388	124.546
3		12.507	54.480	117.911
Average		13.065	55.456	121.744
%RSD		6	2	3
1	20%	12.900	54.754	119.329
2		13.273	55.319	120.891
3		13.313	55.195	120.319
Average		13.162	55.089	120.180
%RSD		2	1	1

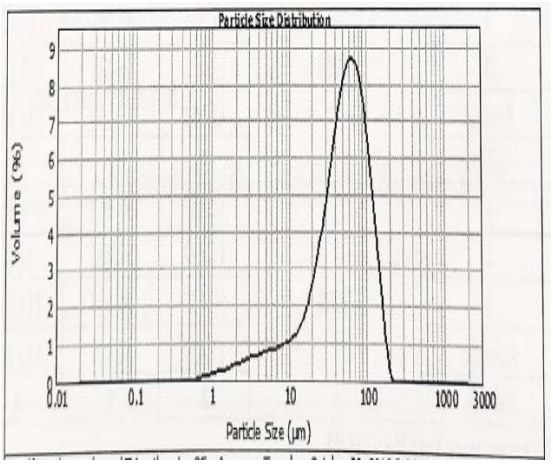

Figure 1. PSD Histogram for Method Precision sample

CONCLUSION

By employing the laser diffraction technique, the particle size distribution for the oral suspension of Sulfamethoxazole/Trimethoprim USP 200 mg/40 mg per 5 ml has been effectively developed and verified. Development trials

were examined for wet dispersion. The particle size distribution of the oral suspension of Sulfamethoxazole/Trimethoprim was determined by using the wet dispersant method, which used water as a dispersion medium. Methods were determined to be precise in the validation process, with a RSD of 8% for d (0.1), 3% for d (0.5), and 2% for d (0.9). In intermediate precision, the % RSD were obtained at 10% for d(0.1), 5% for d(0.5), and 4% for d(0.9). By adjusting the instrumental parameters, such as stirring speed (±200 RPM) and obscuration (5% and 10%), the robustness %RSD was attained within the acceptability requirements for d(0.1), d(0.5), and d(0.9).After compilation and validation, all of the particle size data was determined to be satisfactory. Therefore, Sulfamethoxazole/Trimethoprim oral suspension USP 200 mg/40 mg per 5 ml can be appropriately analysed using the method designed for the particle size method.

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