Analytical Method Development and Validation for Particle Size Distribution of Antiinflammatory Corticosteroid (Loteprednol Etabonate) in Combination Dosage Form

Pramod kumar*[1], Rohit Saraswat[2], Girish Nihalani[3]

[1]Research scholar OPJS University, Churu, Rajasthan, India

[2]Research Guide OPJS University, Churu, Rajasthan, India

[3]Teva Pharmaceuticals USA Inc., FL, USA.

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ABSTRACT

A rapid and robust Particle Size Distribution method was developed and validated for determination of particle size of Loteprednol etabonate in combination of anti-inflammatory corticosteroid and anti-infective combination ophthalmic suspensions by using Malvern Mastersizer 3000. Particle size is a critical quality parameter for pharmaceutical products in which the drug product a solid dosage form or liquid containing undissolved drug substance. In solid or suspension drug products, particle size can have a significant effect on dissolution rates, bioavailability, and/or stability. In such instances, testing for particle size distribution should be carried out using an appropriate procedure, and acceptance criteria should be provided. The present combination ophthalmic suspension having one solubilised drug, and another is suspended form. The undisclosed drug particle would play critical in bioavailability studies. The aim of this paper was to develop a new method to characterize the undissolved drug particle size distribution (PSD), by using Malvern Master Sizer 3000. Water was selected as bring the appropriate dispersant to measure PSD of undisclosed drug particle (Loteprednol Etabonate). Also, the influences of refractive index, Absorption Index, Stirrer speed and measurement time of the particle size distribution were systematically studied. The instrument condition was as follows that are, Particle Refractive Index:1.53, Absorption Index: 0.005, Measurement Duration: 10 Sec, and Stirrer speed 2000 rpm. The optimized Particle Size Distribution method is accurate, simple, repeatable and suitable for determination of the particle size analysis of Loteprednol Etabonate in combination of anti-inflammatory corticosteroid and anti-infective combination ophthalmic dosage form.

INTRODUCTION:

Particle size and size characterization knowledge act as a prerequisite for all the processes which are involved in the production of a formulation. They influence mechanical strength, electrical and thermal properties of the finished product. Within the pharmaceutical industry, the particle size distribution (PSD) of an active pharmaceutical ingredient (API) may have a significant impact on both the manufacturability (flowability, packing properties, mixing, etc.) and quality attributes of the drug product (dissolution rate, bioavailability, content uniformity, etc.)[1]. Massive production losses can occur if particle sizes of the materials being used in the process are not appropriately monitored [1]. Particle size characterization is about describing particle sizes in a formulation that helps in understanding, predicting and optimizing pharmacokinetic properties of that formulation. Accurate determination of particle size is necessary for pharmaceutical industry. It is a physical parameter that must be specified, examined and managed right from the starting material to the finished product. For some new drug substances intended for use in solid or suspension drug products, particle size can have a significant effect on dissolution rates, bioavailability, and/or stability. In such instances, testing for particle size distribution should be carried out using an appropriate procedure, and acceptance criteria should be provided [1]. Despite the modern instrumentation, there are some challenges faced in the field of particle size characterization. An appropriate method development specific to drug type, form, and delivery shall be required. Problems shall be occurring during the analytical method development time and at measurements like agglomeration or de-stabilization. For effective particle size characterization, it is important to understand the suitable instrumentation first. It is advised to use most robust and sensitive technique to obtain accurate results. The main objectives of the present study are to understand the particle size characterization techniques by using commercially used common techniques.

Loteprednol etabonate is an etabonate ester, chloromethyl (8S,9S,10R,11S,13S,14S,17R)-17-ethoxycarbonyloxy-11-hydroxy-10,13-dimethyl-3-oxo-7,8,9,11,12,14,15,16octahydro-6H-cyclopenta[a]phenanthrene-17-carboxylat. It has a role as an anti-inflammatory drug. It derives from a loteprednol. Loteprednol Etabonate is the etabonate salt form of loteprednol, an ophthalmic analog of the corticosteroid prednisolone with anti-inflammatory activity. Loteprednol etabonate exerts its effect by interacting with specific intracellular receptors and subsequently binds to DNA to modify gene expression. This results in an induction of the synthesis of certain anti-inflammatory proteins while inhibiting the synthesis of certain

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inflammatory mediators. Loteprednol etabonate specifically induces phospholipase A2 inhibitory proteins (collectively called lipocortin's), which inhibit the release of arachidonic acid, thereby inhibiting the biosynthesis of potent mediators of inflammation, such as prostaglandins and leukotrienes. [2].

This compound was designed based on prednisolone and to reduce side effects, carboxylic ester functionality was introduced at 17b-position, in the expectation that hydrolysis by non-specific esterases would transform it into the indicative steroid carboxylic acid metabolite. Loteprednol etabonate is used in the topical management of inflammatory and allergic disorders of the eye. It is usually employed as eye drops containing 0.2 or 0.5%. Coffey and co-workers describe a novel ophthalmic gel formulation of loteprednol etabonate in the treatment of ocular inflammatory conditions. Prolonged application to the eye of preparations containing corticosteroids has caused raised intra-ocular pressure and reduced visual function. A literature survey revealed that there no such methods were available for determination of particle size distribution of Loteprednol Etabonate bulk drug as well ophthalmic dosage form [3].

This paper describes a simple, precise, accurate and robust, specific to particle size distribution of Loteprednol etabonate in combination eye drops. The proposed PSD method utilizes economically available common instrument and solvent system. The method was validated as per International Conference on Harmonization (ICH) [4] suggestions.

Loteprednol etabonate:

$C_{24}H_{31}ClO_7$ Mol. Wt. 466.96
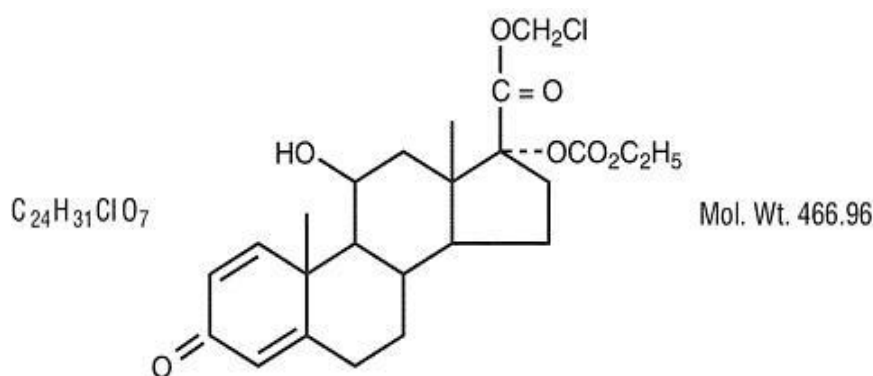
Chemical name: Chloromethyl 17α-[(ethoxycarbonyl)oxy]-11β-hydroxy-3-oxoandrosta-1,4-diene-17β-carboxylate

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INSTRUMENTATION AND PRINCIPLE:

For a successful Particle Size Distribution method development, the understanding of the basic principles of laser diffraction is essential. Laser diffraction is an ensemble particle-sizing technique, which means it provides a result for the whole sample, rather than building up distributions from data for individual particles. Particles illuminated in a collimated laser-beam scatter light over a range of angles. Large particles generate a high scattering intensity at relatively narrow angles to the incident beam, while smaller particles produce a lower intensity signal but at much wider angles. Using an array of detectors, laser-diffraction analyzers record the pattern of scattered light produced by the sample. The Mastersizer range of laser diffraction particle size analyzers set the standard for delivering rapid, accurate particle size distributions for both wet and dry dispersions. From assessing product uniformity and solubility, through to optimizing packing density to improve final product performance and controlling powder flowability to increase manufacturing efficiency, particle size analysis is critical to understanding and controlling a wide range of properties. In a laser diffraction measurement, a laser beam passes through a dispersed particulate sample and the angular variation in intensity of the scattered light is measured. Large particles scatter light at small angles relative to the laser beam and small particles scatter light at large angles. The angular scattering intensity data is then analyzed to calculate the size of the particles that created the scattering pattern using the Mie theory of light scattering. The particle size is reported as a volume equivalent sphere diameter.

MASTERSIZER 3000:

The Mastersizer 3000 is the latest generation of the world's most widespread particle sizing instrument, used by many thousands of companies and research institutes across a wide range of industries. Malvern's considerable experience and applications know-how has gone into every stage of the design of the Mastersizer 3000 instrument, from fundamental particle sizing performance right through to user ergonomics and method advice. A completely new optical core design delivers fast measurement times for high sample throughput and a measurement size range from 10 nm to 3.5 mm. Combined with a range of wet and dry dispersion accessories this opens up more applications than ever before. The Mastersizer 3000 uses the technique of laser diffraction to measure particle size distributions from 10 nm up to 3.5 mm [5].

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LASER DIFFRACTION:

In a laser diffraction measurement, a laser beam passes through a dispersed particulate sample and the angular variation in intensity of the scattered light is measured. Large particles scatter light at small angles relative to the laser beam and small particles scatter light at large angles. The angular scattering intensity data is then analysed to calculate the size of the particles that created the scattering pattern using the Mie theory of light scattering. The particle size is reported as a volume equivalent sphere diameter [5].
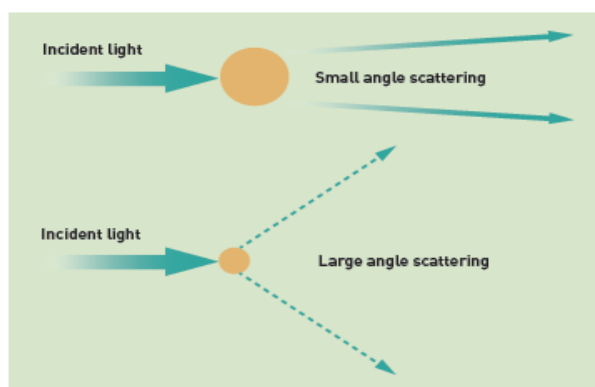
MATERIALS AND METHODS:

Malvern Mastersizer 3000 equipped with Hydro MV accessory and Mastersizer software version no. 1.70 was used. A Milli-Q purification system (Millipore, Bedford, MA, USA) was used to further purify demineralized water. Loteprednol Etabonate was purchased from Sigma-Aldrich. Loteprednol etabonate and tobramycin ophthalmic suspension was purchased from market.

Mastersizer 3000 Instrument specification:

Mastersizer 3000 is equipped with Hydro MV accessory. Hydro MV - A medium volume automated dispersion unit specifically designed for applications where sample is in short supply and/or non-aqueous dispersants are necessary [5].

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Parameter	Specification
Pump speed range	0-3500 rpm
Pump speed resolution	+/- 10 rpm
Pump speed accuracy	+/- 50 rpm
Maximum flow rate	2.0L/min
Sonication power & frequency	40W max, 40kHz (nominal)
Maximum volume	120mL
Materials in contact with sample	316 stainless Borosilicate glass Tygon® FKM (cell seal only - FFKM upgrade available) PTFE PEEK FEP Titanium Nitride Aluminium (tubing connectors only) Acrylic (splash guard only)
Maximum particle size	1500μm
Minimum time between measurements	less than 60 sec
Dimensions	280mm x 180mm x 300mm (L x W x H)
Mass	5kg

RESULTS:

Method development:

The primary goal was to develop a method to obtain the most stable, reproducible, consistent method. Loteprednol Etabonate active materials solubility is about 0.000693 mg/mL [6]. Hence saturation solution of Loteprednol Etabonate in water was selected as dispersant. Varies trials were tried for optimization of stirring speed, RI and obscuration range. The finalised method parameters were as follows.

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Sr. No	Instrument Parameter	Value
1	Particle Refractive Index	1.53
2	Absorption Index	0.005
3	Dispersant Name	Water
4	Dispersant Refractive Index	1.330
5	Level Sensor Threshold	3
6	Measurement Duration	10 sec.
7	Number of Measurements	3
8	Report Average of Measurements	Yes
9	Obscuration	About 15.0%
10	Stirrer speed	2000 rpm
11	Distribution model	Volume based distribution

Sample preparation: Used as such formulation product.

Particle Size Distribution Measurement Procedure:

Clean the tank cell thoroughly with purified water until the Detector Energy indicator shows below 100 and in anti-parabolic manner. Fill the tank with dispersant, align the mentioned instrument parameters and perform background check. Shake the sample well for uniform dispersion. Take some sample in dropper and add dropwise to achieve desired obscuration limit (not more than 10.0%). Start the measurement and wait till the given number of measurements (3) is completed. Create average of the 3 measurements and report average results.
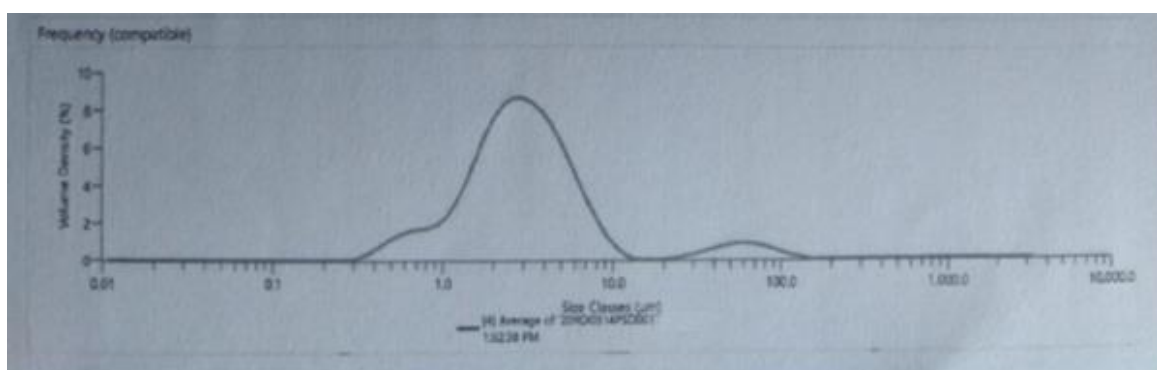

Figure No. 1: Typical histogram of particle size distribution

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Validation:

After successful method development, method validation was performed. For method validation the following parameters were considered [8].

1. Method precision

2. Intermediate precision

3. Robustness

3.1 Change in the stirrer speed to ± 200 rpm

3.2 Change in the Obscuration % to ± 5%

3.3 Change in the measurement duration ±2sec.

Precision:

Repeatability should be evaluated for assessment of precision. Repeatability was determined by six repetitive sample preparations of Loteprednol and tobramycin formulation product. The particle size distribution of six samples preparation were determined as per above method and recorded the particle size for d(0.1), d(0.5) and d(0.9).

Acceptance criteria: The % RSD of d(0.1) particle size values is should not be more than 30, for d(0.9) particle size values is should not more than 30 and d(0.5) particle size values is should not more than 20[7]. The results were tabulated below.

Table No. 1: Method precision results

Sample preparation	Avg. (n=3) Particle size (in μm)		
	d(0.1)	d(0.5)	d(0.9)
Preparation - 1	1.085	2.344	5.916
Preparation – 2	1.095	2.519	5.473
Preparation – 3	1.094	2.692	5.531
Preparation – 4	1.019	2.466	5.863
Preparation – 5	1.041	2.682	5.377
Preparation – 6	1.104	2.623	5.999
Average	**1.073**	**2.554**	**5.693**
% RSD	**3.22**	**5.35**	**4.63**

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RESULTS: The % RSD for d(0.1), d(0.5) and d(0.9) are well within the acceptance criteria. The % RSD for (0.1) is 3.22, for d(0.9) is 4..63 and d(0.5) is 5.35.

Intermediate Precision:

Intermediate precision was performed on different day. The Intermediate precision of particle size distribution were determined for six sample preparations as per above method and recorded the particle size for d(0.1), d(0.5) and d(0.9).

Acceptance criteria: The % RSD of d(0.1) particle size values is should not be more than 30, for d(0.9) particle size values is should not more than 30 and d(0.5) particle size values is should not more than 20[7]. The cumulative % RSD of d(0.1) particle size values is should not be more than 30, for d(0.9) particle size values is should not more than 30 and d(0.5) particle size values is should not more than 20. The combined method precision and intermediate precision results were tabulated below.

Table No. 2: Intermediate precision results

Sample preparation	Avg. (n=3) Particle size (in µm)		
	d(0.1)	d(0.5)	d(0.9)
IP Preparation - 1	1.024	2.639	5.352
IP Preparation – 2	1.092	2.515	5.521
IP Preparation – 3	1.178	2.213	5.645
IP Preparation – 4	1.055	2.399	5.521
IP Preparation – 5	1.127	2.401	5.638
IP Preparation – 6	1.089	2.788	5.484
Average	**1.094**	**2.493**	**5.527**
% RSD	**4.94**	**8.11**	**1.96**
MP Preparation - 1	1.085	2.344	5.916
MP Preparation – 2	1.095	2.519	5.473
MP Preparation – 3	1.094	2.692	5.531
MP Preparation – 4	1.019	2.466	5.863
MP Preparation – 5	1.041	2.682	5.377
MP Preparation – 6	1.104	2.623	5.999
Cumulative Average	**1.084**	**2.523**	**5.610**
Cumulative % RSD	**4.12**	**6.64**	**3.76**

RESULTS: The % RSD for d(0.1), d(0.5) and d(0.9) are well within the acceptance criteria. The % RSD for (0.1) is 3.22, for d(0.9) is 4..63 and d(0.5) is 5.35.

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The cumulative % RSD for d(0.1)is 4.12, for d(0.9) id 3.76 and for d(0.5) is 6.64. All the results were well within the acceptance criteria.

Robustness:

As per ICH guidelines [4], the robustness of an analytical method is its ability to withstand small but deliberate changes in the experimental variables. In this study, the robustness was evaluated by an experimental design examining the simultaneous influence of change in stirring speed, change in the Obscuration and change in the measurement duration on the determination of particle size distribution. Robustness was performed by varying the above said parameters and particle size distribution determined in triplicates. The results were discussed in the following tables.

Acceptance criteria:

The % RSD for d(0.1) particle size values is should not be more than 30, for d(0.9) particle size values is should not more than 30 and d(0.5) particle size values is should not more than 20 for all variable conditions in robustness. The cumulative % RSD with method precision values and variable condition of robustness parameter data of d(0.1) particle size values is should not be more than 30, for d(0.9) particle size values is should not more than 30 and d(0.5) particle size values is should not more than 20.

Table No. 3: Robustness-1 (Change in stirring speed 1800 rpm results)

Sample preparation	Avg. (n=3) Particle size (in µm)		
	d(0.1)	**d(0.5)**	**d(0.9)**
Robustness -1 Preparation - 1	1.062	2.654	5.486
Robustness -1 Preparation - 2	1.115	2.315	5.631
Robustness -1 Preparation - 3	1.165	2.346	5.721
Average	**1.114**	**2.438**	**5.613**
% RSD	**4.62**	**7.69**	**2.11**
MP Preparation - 1	1.085	2.344	5.916
MP Preparation – 2	1.095	2.519	5.473
MP Preparation – 3	1.094	2.692	5.531
MP Preparation – 4	1.019	2.466	5.863
MP Preparation – 5	1.041	2.682	5.377
MP Preparation – 6	1.104	2.623	5.999
Cumulative Average	**1.087**	**2.516**	**5.666**
Cumulative % RSD	**3.94**	**6.13**	**3.89**

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RESULTS: The % RSD for d(0.1), d(0.5) and d(0.9) are well within the acceptance criteria. The % RSD for (0.1) is 4.62, for d(0.9) is 2.11 and d(0.5) is 7.69.

The cumulative % RSD for d(0.1)is 3.94, for d(0.9) id 3.89 and for d(0.5) is 6.13. All the results were well within the acceptance criteria.

Table No. 4: Robustness-2 (Change in stirring speed 2200 rpm results)

Sample preparation	Avg. (n=3) Particle size (in µm)		
	d(0.1)	**d(0.5)**	**d(0.9)**
Robustness -2 Preparation - 1	1.025	2.664	5.586
Robustness -2 Preparation - 2	1.125	2.456	5.784
Robustness -2 Preparation - 3	1.118	2.546	5.346
Average	**1.089**	**2.555**	**5.572**
% RSD	**5.12**	**4.08**	**3.94**
MP Preparation - 1	1.085	2.344	5.916
MP Preparation – 2	1.095	2.519	5.473
MP Preparation – 3	1.094	2.692	5.531
MP Preparation – 4	1.019	2.466	5.863
MP Preparation – 5	1.041	2.682	5.377
MP Preparation – 6	1.104	2.623	5.999
Cumulative Average	**1.078**	**2.555**	**5.653**
Cumulative % RSD	**3.70**	**4.69**	**4.30**

RESULTS: The % RSD for d(0.1), d(0.5) and d(0.9) are well within the acceptance criteria. The % RSD for (0.1) is 5.12, for d(0.9) is 3.94 and d(0.5) is 4.08.

The cumulative % RSD for d(0.1)is 3.70, for d(0.9) id 4.30 and for d(0.5) is 4.69. All the results were well within the acceptance criteria.

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Table No. 5: Robustness-3 (Change in obscuration 10% results)

Sample preparation	Avg. (n=3) Particle size (in µm)		
	d(0.1)	d(0.5)	d(0.9)
Robustness -3Preparation - 1	1.165	2.715	5.845
Robustness -3Preparation - 2	1.095	2.541	5.542
Robustness -3Preparation - 3	1.254	2.645	5.196
Average	**1.171**	**2.634**	**5.528**
% RSD	**6.80**	**3.32**	**5.87**
MP Preparation - 1	1.085	2.344	5.916
MP Preparation – 2	1.095	2.519	5.473
MP Preparation – 3	1.094	2.692	5.531
MP Preparation – 4	1.019	2.466	5.863
MP Preparation – 5	1.041	2.682	5.377
MP Preparation – 6	1.104	2.623	5.999
Cumulative Average	**1.106**	**2.581**	**5.638**
Cumulative % RSD	**6.23**	**4.77**	**4.91**

RESULTS: The % RSD for d(0.1), d(0.5) and d(0.9) are well within the acceptance criteria. The % RSD for (0.1) is 6.80, for d(0.9) is 5.87 and d(0.5) is 3.32.

The cumulative % RSD for d(0.1)is 6.23, for d(0.9) id 4.91 and for d(0.5) is 4.77. All the results were well within the acceptance criteria.

Table No. 6: Robustness-4 (Change in obscuration 20% results)

Sample preparation	Avg. (n=3) Particle size (in µm)		
	d(0.1)	d(0.5)	d(0.9)
Robustness -4 Preparation - 1	1.224	2.785	5.912
Robustness -4 Preparation - 2	1.119	2.552	5.346
Robustness -4 Preparation - 3	1.108	2.607	5.117
Average	**1.150**	**2.648**	**5.458**
% RSD	**5.57**	**4.60**	**7.50**
MP Preparation - 1	1.085	2.344	5.916
MP Preparation – 2	1.095	2.519	5.473
MP Preparation – 3	1.094	2.692	5.531
MP Preparation – 4	1.019	2.466	5.863
MP Preparation – 5	1.041	2.682	5.377
MP Preparation – 6	1.104	2.623	5.999
Cumulative Average	**1.099**	**2.586**	**5.615**
Cumulative % RSD	**5.20**	**5.12**	**5.60**

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RESULTS: The % RSD for d(0.1), d(0.5) and d(0.9) are well within the acceptance criteria. The % RSD for (0.1) is 5.57, for d(0.9) is 7.50 and d(0.5) is 4.60.

The cumulative % RSD for d(0.1)is 5.20, for d(0.9) id 5.60 and for d(0.5) is 5.12. All the results were well within the acceptance criteria.

Table No. 7: Robustness-5 (Change in Measurement Duration -8 sec results)

Sample preparation	Avg. (n=3) Particle size (in μm)		
	d(0.1)	d(0.5)	d(0.9)
Robustness -5 Preparation - 1	1.119	2.642	6.012
Robustness -5 Preparation - 2	1.208	2.574	5.741
Robustness -5 Preparation - 3	1.138	2.496	5.426
Average	**1.155**	**2.571**	**5.726**
% RSD	**4.06**	**2.84**	**5.12**
MP Preparation - 1	1.085	2.344	5.916
MP Preparation – 2	1.095	2.519	5.473
MP Preparation – 3	1.094	2.692	5.531
MP Preparation – 4	1.019	2.466	5.863
MP Preparation – 5	1.041	2.682	5.377
MP Preparation – 6	1.104	2.623	5.999
Cumulative Average	**1.100**	**2.560**	**5.704**
Cumulative % RSD	**4.96**	**4.46**	**4.47**

RESULTS: The % RSD for d(0.1), d(0.5) and d(0.9) are well within the acceptance criteria. The % RSD for (0.1) is 4.06, for d(0.9) is 5.12 and d(0.5) is 2.84.

The cumulative % RSD for d(0.1)is 4.96, for d(0.9) id 4.47 and for d(0.5) is 4.46. All the results were well within the acceptance criteria.

Table No. 8: Robustness-6 (Change in Measurement Duration -12 sec results)

Sample preparation	Avg. (n=3) Particle size (in μm)		
	d(0.1)	d(0.5)	d(0.9)
Robustness -6 Preparation - 1	1.287	2.715	5.941
Robustness -6 Preparation - 2	1.324	2.55	5.716
Robustness -6 Preparation - 3	1.214	2.485	5.346
Average	**1.275**	**2.583**	**5.668**
% RSD	**4.39**	**4.59**	**5.30**
MP Preparation - 1	1.085	2.344	5.916
MP Preparation – 2	1.095	2.519	5.473
MP Preparation – 3	1.094	2.692	5.531
MP Preparation – 4	1.019	2.466	5.863
MP Preparation – 5	1.041	2.682	5.377
MP Preparation – 6	1.104	2.623	5.999
Cumulative Average	**1.140**	**2.564**	**5.685**
Cumulative % RSD	**9.50**	**4.84**	**4.52**

RESULTS: The % RSD for d(0.1), d(0.5) and d(0.9) are well within the acceptance criteria. The % RSD for (0.1) is 4.39, for d(0.9) is 5.30 and d(0.5) is 4.59.

The cumulative % RSD for d(0.1)is 9.50, for d(0.9) id 4.52 and for d(0.5) is 4.84. All the results were well within the acceptance criteria.

DISCUSSION

The method for determination of particle size distribution of Loteprednol Etabonate in combination product Loteprednol Etabonate and Tobramycin Ophthalmic dosage formulation was developed and validated. During development varies trials were taken by changing the stirring speed, Particle RI, Obscuration and measurement delay time etc. Finally, the method was optimized with above said method parameters. Further method suitability was confirmed by method validation performing parameters such as Precision, Intermediate Precision and Robustness.

CONCLUSION

The present method development and method validation for particle size distribution of Loteprednol Etabonate in Loteprednol Etabonate and Tobramycin ophthalmic dosage form is found to beprecise, specific, rapid and robust. All the data has been compiled and found to be satisfactory. Hence, the developed method for the determination of particle size distribution

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of Loteprednol Etabonate in Loteprednol Etabonate and Tobramycin ophthalmic dosage form can be suitably used for analysis. Therefore, this method could easily be used in a wide range of analytical laboratories.

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