Automated Foreign Particulate Matter Testing for Pharmaceutical Inhalation Products

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Summary

Quality by design promotes Foreign Particulate Matter (FPM) testing of inhalation pharmaceutical products during the development and manufacturing process. Foreign particles meeting specified size criteria captured from emitted doses of inhaled product have traditionally been counted using manual microscope techniques. However such methods can be time consuming and open to subjectivity.
An automated image analysis method (Morphologi G3, Malvern Instruments) allows the detection of FMP in inhaled products down to 2 µm (longest length) in a reproducible, routine manner following a Standard Operating Procedure (SOP). Results detailing the counts of particles meeting specific size criteria are given at the end of each analysis and a significant amount of morphological information on every particle detected is also provided.

Introduction

Foreign Particulate Matter (FPM) is extraneous, randomly-sourced, solid, organic and inorganic, contaminating substances that may be found in pharmaceutical inhalation devices. Typical FPM in pharmaceutical inhalation devices present at the end of manufacturing or generated by abrasion or shearing during device activation may include glass, transparent synthetic fibres, stainless steel, rubber, aluminum and plastic particles. The US Food and Drug Administration (FDA) requested that FPM in pharmaceutical inhalation devices be the subject of quality control limits in the size ranges <10µm, 10-100µm, and >100µm. More recently, the International Pharmaceutical Aerosol Consortium on Regulation and Science (IPAC-RS) has summarised the progression of regulatory recommendations for FPM in Orally Inhaled and Nasal Drug Products (OINDP). They have proposed approaches for developing safety thresholds for FPM, and best practices for managing quality and safety of OINDP with respect to FPM, based on Quality by Design (1,2).

Procedures for FPM testing often involve the capture of an emitted dose of the inhaled product, followed by the dissolution of active pharmaceutical ingredient (API) and any excipients. The remaining FPM is deposited onto a filter and is counted by manual methods using an optical light microscope. Such analyses can take up to a day to perform. The detection of very fine FPM particles (<5 microns) can also be difficult and is open to human subjectivity. In this paper, we present a method for FPM detection for inhalation products using an automated, image analysis system (Morphologi® G3, Malvern Instruments). This technique is shown to provide accurate, reproducible quantification of FPM down to as small as 2µm in size (longest length), in less than an hour. Additionally, a significant amount of morphological information is obtained for every particle detected, aiding identification of the source of contamination.

Sample Preparation

Eight emitted doses of the inhaled product were captured, and the active pharmaceutical ingredient (API) and excipients were dissolved and subsequently removed based on their selective solubility. The remaining FPM was collected on a mixed cellulose ester filter. A filter blank was performed prior to testing the product to demonstrate that the equipment and solutions used did not contribute a significant number of particles. All sample preparations were performed in a particle free atmosphere.

Sample Analysis

A standard operating procedure (SOP) was set up on the Morphologi G3 image analysis system which defined all the variables for the analyses. These included the light intensity, threshold and a scan area to allow the whole of the wetted area of the filter to be analysed. The system was also set to perform z-stacking on every field of view to ensure that even small particles that may be in the well of a filter paper (after filtration through a mesh) are captured. Classifications were also defined in the SOP so that the particles were automatically counted into the size categories of interest. These were:

Particles with length ≥ 2 < 10 µm
Particles with length ≥ 10 < 25 µm
Particles with length ≥ 25 < 100 µm
Particles with length > 100 µm

The prepared filter paper containing the FPM was placed in the instrument's filter holder which stretches the paper flat. The analysis was performed automatically by pressing start and took approximately 20 minutes. It should be noted at this time the analyses were not carried out in a controlled clean room environment.

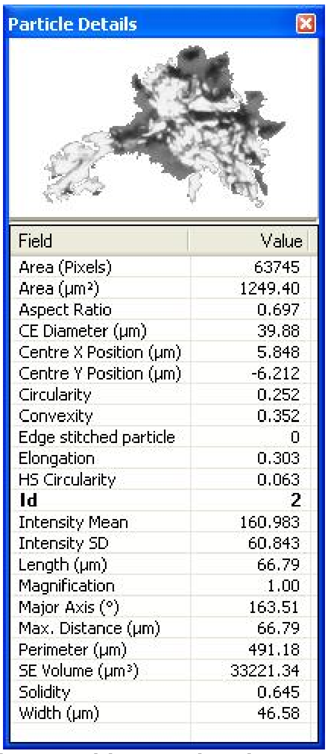
Results

The results of 5 repeat FPM tests on a prepared filter paper are shown in Table 1. The results show the number of FMP particles counted in each of the size classes of interest. The 5 repeat results show the good reproducibility of the analysis.

Table 1: Results of FPM testing of a filter (5 repeats)

Sample Name	Total Particles	2-10µm	10-25µm	25-100µm	>100µm
Filter B Scan 1	13893	13025	712	146	10
Filter B Scan 2	13853	12976	714	153	10
Filter B Scan 3	14211	13334	716	152	9
Filter B Scan 4	13952	13108	686	149	9
Filter B Scan 5	13855	12982	711	152	10
Mean	13953	13085	708	150	10
Standard Deviation	150	149	12	3	1
RSD %	1.07	1.14	1.74	1.92	5.71

For every particle analysed detailed information in terms of many morphological parameters is provided, an example of which is shown in figure 1.



Field	Value
Area (Pixels)	63745
Area (µm²)	1249.40
Aspect Ratio	0.697
CE Diameter (µm)	39.88
Centre X Position (µm)	5.848
Centre Y Position (µm)	-6.212
Circularity	0.252
Convexity	0.352
Edge stitched particle	0
Elongation	0.303
HS Circularity	0.063
Id	**2**
Intensity Mean	160.983
Intensity SD	60.843
Length (µm)	66.79
Magnification	1.00
Major Axis (°)	163.51
Max. Distance (µm)	66.79
Perimeter (µm)	491.18
SE Volume (µm³)	33221.34
Solidity	0.645
Width (µm)	46.58

Figure 1: An example particle image with associated reported morphological parameters.

Additionally a composite image and a plot of x-position vs y-position allow the position of any particle to be identified and provide a permanent electronic record of the entire filter. An example is shown in Figure 2.

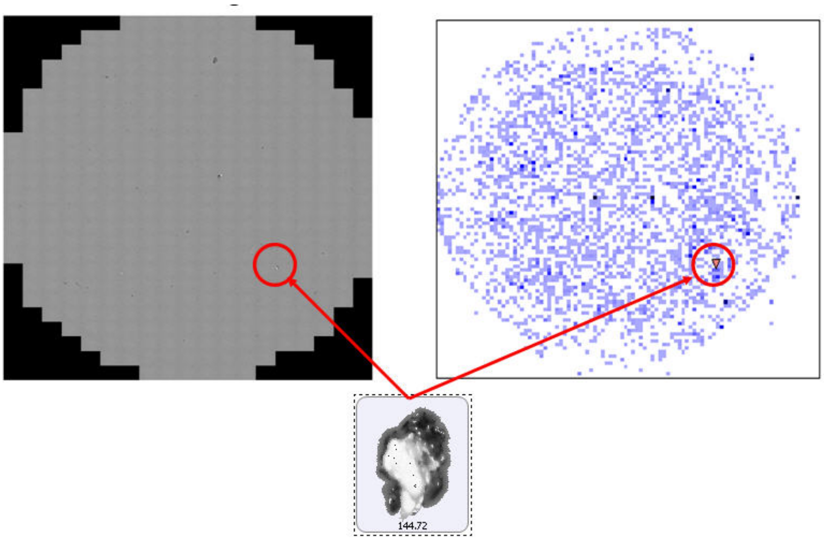


Figure 2: Composite image and x-position vs y-position plot which allows the position of the particle to be identified and provides a permanent electronic record of the filter sample.

Conclusion

In summarising the progress of regulatory recommendations for FPM in OINDP, the IPAC-RS has demonstrated the need to enumerate and characterise foreign particulate matter during development studies (1) especially in order to follow concepts such as Quality By Design proposed by the FDA.

Traditionally optical microscopy methods have been time consuming and subjective particularly when counting particles less than 5 µm in size therefore making accurate statistical data comparisons difficult. However the recent automation of microscope based-techniques incorporating image analysis, powerful software and improved sample presentation has allowed such testing to be carried out in a fast, repeatable, routine manner. The instrumentation described in this paper combines high quality objectives with a high resolution scientific grade camera which allows confident analysis of particles down to 2 µm in size since images for these small particles contain approximately 30 pixels. Therefore rigorous statistical analysis of process batches and stability batches can be carried out and specifications for the number of particles allowed in each class for commercial inhalation drug formulations can then be established based on the development study results and safety considerations.

References

(1) Best Practices for Managing Quality and Safety of Foreign Particles in Orally Inhaled and Nasal Drug Products, and an Evaluation of Clinical Relevance, Pharmaceutical Research, Vol. 24, No. 3, March 2007.

(2) Foreign Particles Testing in Orally Inhaled and Nasal Drug Products, Pharmaceutical Research, Vol. 21, No. 12, December 2004.