

APPLICATION NOTE

195 Stafford Road West
Ottawa, Ontario, Canada K2H 9C1
Tel: (613) 829-2772 – Fax: (613) 829-4921
Email: info@brightwelltech.com

MFI™ for Injectable and Ophthalmic Solutions

USP 788 and 789 are established standards which define the maximum allowable limits for particulate matter in injectable and ophthalmic solutions. Test procedures call for the analysis of fluid samples using single particle light obscuration and, in the event of sample failure or if obscuration is not practical, for filtration and microscopic examination.

Light obscuration provides an indirect measurement of the equivalent circular diameter for each particle based on a calibration curve generated using polystyrene spheres. To the extent that particles in real-world solutions are composed of different materials and, are often far from spherical, errors in sizing/counting are inevitable. Filtration and microscopic examination is labor intensive, and operator subjectivity in assigning a diameter to each particle is difficult to avoid.

The objectives of USP 788 and 789 are patient protection. The standards are not intended to provide further insight into the nature and origin of the suspended particulates themselves. However this information is of prime importance to process specialists responsible for formulation, bulk handling, storage stability and preventing contamination by injection devices. MFI™ is a new technique which employs digital imaging of a flowing sample stream for analyzing solutions. MFI™ instruments provide highly sensitive detection, counting, and sizing of each individual particle combined with an automatic image capture and shape analysis capability. MFI™ instruments can improve product quality and process yield through more rigorous incoming and in-process inspection and, with the additional insights available from an imaging platform, are useful for diagnosing and preventing particle contamination.

The MFI™ Advantage

Material and Shape Independence: Unlike many indirect particle size measurement technologies, the direct, pixel based imaging technique employed in MFI makes no assumptions of particle size or shape. MFI™ is well suited for heterogeneous outlier populations commonly found in injectable and ophthalmic solutions. No calibration by the user is required.

Concentration Measurement: MFI™ instruments provide highly sensitive detection, counting, and sizing of each individual particle present in each image frame. Each frame represents an accurately known volume of sample, permitting direct measurement of particle concentration.

Selective Image Capture: The selective image capture feature in MFI™ allows a user to store images of any particles detected during the run. These images serve to confirm numerical results and are valuable for process control, quality control, diagnostics and troubleshooting.

Comprehensive Morphological Analysis: Stored images may be analyzed using the MFI™ morphological analysis module, providing measurement of ECD, Feret's diameter, area, perimeter, circularity and transparency. These additional parameters may be conveniently presented in the form of histograms or scatterplots. This analysis provides further insight into the particle nature and origin.

Speed and Convenience: MFI™ analyzers are easy to operate and analyze multiple image frames per second providing a full population analysis in less than 5 minutes.

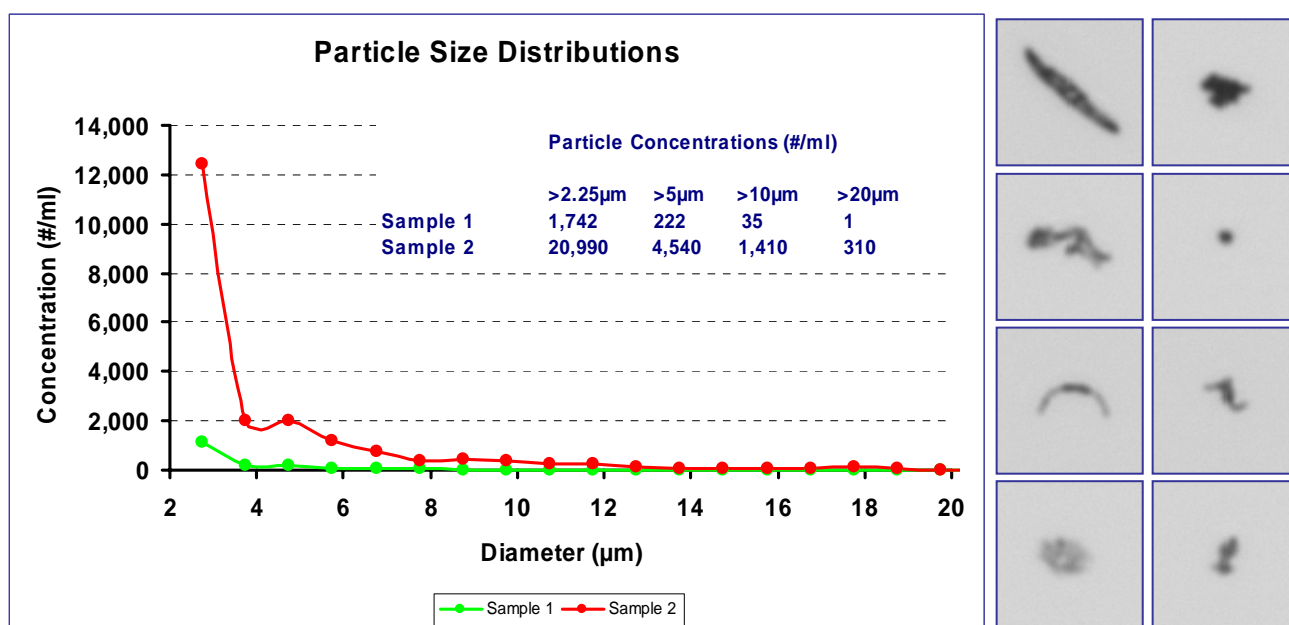
Direct Observation: During analysis, image frames are displayed providing immediate visual feedback on the nature of a particle population.

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MFI™ Sizing, Counting, Image Capture

The DPA4100 MFI™ system supports operation at two different magnification set points depending on the size range of interest (0.75-100µm or 2.25-400µm). Images may be stored selectively based on detection of particles falling into user-specified size ranges, or sequentially as a function of time. The results below are an example of a DPA4100 analysis of two different parenteral samples.



MFI™ Morphology Analysis

In addition to measuring the size and concentration of outlier particles, MFI™ can measure the morphological characteristics of the suspended particulate (equivalent circular diameter, Feret's diameter, area, perimeter, circularity, and transparency) using the captured images. Powerful software tools including variable thresholding, histograms, scatter plots, and fully exportable data sets permit comprehensive comparisons across samples and more advanced particulate diagnostics.

Summary

MFI™ instruments provide highly sensitive detection, counting, and sizing of each individual particle combined with an automatic image capture and shape analysis capability. These features provide further insight into the nature and origin of suspended particulates and can improve product quality and process yield, both through more rigorous incoming and in-process inspection and, through the additional insight gained for process development and troubleshooting.