

ISO 8871-3 - Measuring particle release from stoppers with Hound

Introduction

The ISO 8871-3 guidelines are widely used to detect fibers and other particulate contamination on rubber stoppers used in pharmaceutical manufacturing. Particulate matter on these stoppers can be released into a vial. The number of particle contaminants found on rubber stoppers has a direct bearing on the reject levels of parenterals produced.

Hound can quickly determine the number and size of particles on a rubber stopper. Hound is an automated system that uses microscopy to identify, count, and size particles in compliance with 21 CFR Part 11 (Figure 1). Additionally, particles can be identified by Raman or Laser-Induced Breakdown Spectroscopy. By using Hound to quantify particles on rubber stoppers during manufacturing or during vialing of drug product, parenteral rejection rate can be predicted and therefore reduced.

Methods

10 rubber stoppers were immersed in 100 mL of 0.1% Tween solution and shaken for 10 minutes to release all particles. The resulting solution was filtered through a 0.8 μm gold coated filter round. The effective filtration area (EFA) on the filter round was 10 mm. Before and after analysis of the particle containing solution, blank controls were run on the Hound to ensure system cleanliness. The entire EFA of the filter round was analyzed by Hound to determine particle counts, sizing, and shape with a resolution of 5 pixels/particle.

Results

568 fields of view were captured to scan the entire 10 mm EFA in 15 minutes (Figure 2). On the scan shown in Figure 2, many small particles can be seen, but only one large particle is present. The large particle was 428.1 μm in size and spanned



Figure 1: Hound images, counts, sizes and identifies particles with Raman and/or Laser-Induced Breakdown Spectroscopy.

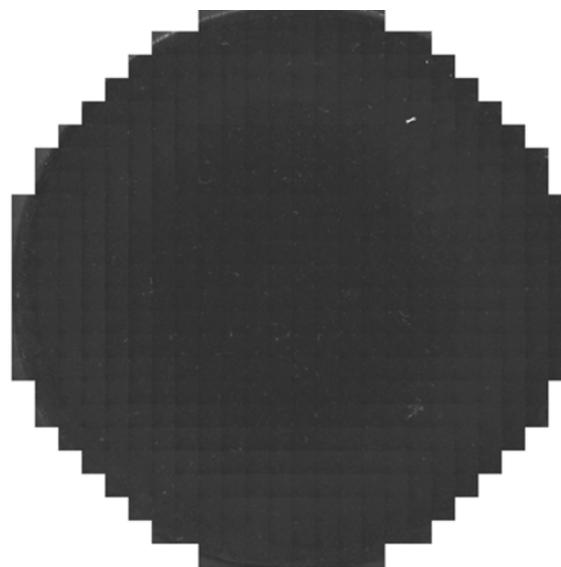


Figure 2: The combination of the 568 individual fields of view captured by Hound to image the entire 10 mm effective filtration area of the filter round. Particles appear white, while the filter round background appears black.

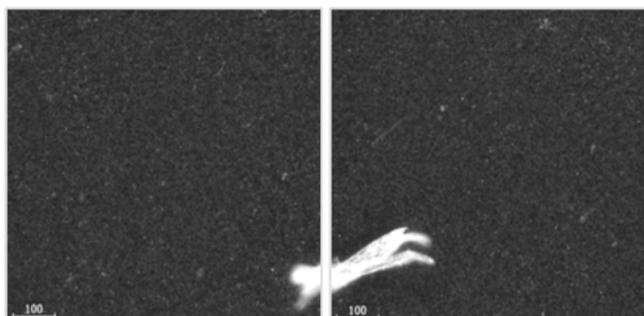


Figure 3: Two fields of view that each contain a partial image of the largest fibrous particle found on the 10 stoppers analyzed (428.1 μm). The two images are automatically stitched by the Hound software to treat this fiber as a single particle.

two fields of view (Figure 3). Fibers and particles that span multiple fields of view are automatically stitched together by the Hound software and their size and morphology are recognized from stitched images.

In total 2,173 particles were counted from the 10 stoppers analyzed. The size distribution of these particles is shown in Table 1.

Distribution (μm)				
10-25	25-50	50-100	100-250	≥ 250
2,009	123	32	8	1

Table 1: Size distribution of the particle count per 10 stoppers.

As seen in the scan of the entire EFA, most of the particles are small, with 2,009 particles in the range of 10–25 μm and another 123 particles in the range of 25–50 μm . Hound was able to determine total particle counts and size distributions of particle contaminants on the 10 rubber stoppers analyzed. Hound can be used as a screening tool to reject stopper types with too many particles to prevent rejection of parenteral drugs later in the production process.

Summary

Hound can determine and document the number of particles present on rubber stoppers in accordance with ISO 8871-3 guidelines and in compliance with 21 CFR Part 11. In a matter of minutes, Hound can automatically provide a rubber stopper or pharmaceutical manufacturer valuable information regarding the cleanliness of the rubber stoppers produced and used. Hound can recognize and characterize both particles and fibers through high powered microscopy and spectroscopy. In cases where further analysis and identification of these particles is desirable, Hound can automatically recognize the morphology and identify the chemical composition of particles with Raman spectroscopy or elemental composition with Laser-Induced Breakdown Spectroscopy.



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