AI-Driven Subvisible Particle Classification in Pharmaceutical Excipients Using FlowCam Microscopy

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INTRODUCTION

The presence of particles, either extrinsic (glass, rubber, fibers), intrinsic (drug crystals, excipient incompatibilities) or inherent (protein aggregates, silicone oil droplets) in a drug product can affect safety and efficacy, stability and regulatory compliance. Excipients often constitute the bulk of pharmaceutical formulations and therefore represent a potential source of particulate contaminants. The ability to identify particulates enables faster and more informed investigations into formulation issues. We investigate the use of sub visible particle analysis using FlowCam Imaging Microscopy and Visual AI for automated, image-based identification and classification of particles in the unfiltered solutions of sulfobutylether beta cyclodextrin (SBECD) from different sources.

OBJECTIVES

1. Create libraries of common particle images, such as filter materials (nylon, PTFE), silicone oil, weigh paper, glass fragments and plastic to enable automated classification of particles.
2. Evaluate unfiltered solutions of SBECD from different sources, identify, classify and sort the particle images using the library filters.

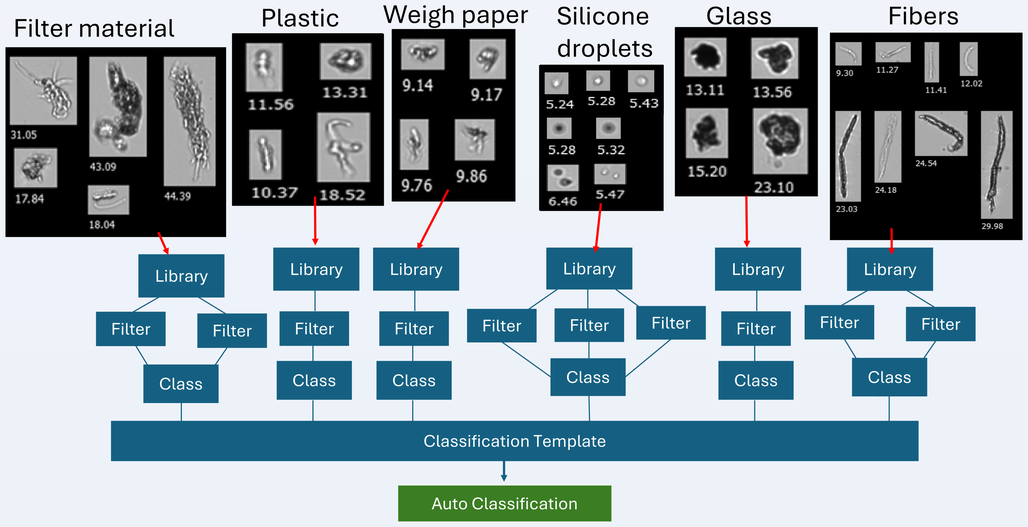
MATERIALS AND METHODS

Particle Library Creation

Reference particle image libraries were generated by mechanically abrading representative product-contact materials with a cleaned razor blade and transferring the resulting particulates into vials containing nanopure water. Materials sampled included gossamer weighing paper, nylon and PTFE membrane filter media, and polypropylene. Silicone droplets were detected using Yokogawa Visual AI software and glass fragment images were determined from reference material.

Samples were analyzed on a Yokogama Fluid Imaging Technologies FlowCam® using the 10× objective. Acquisition capture settings were iteratively optimized to minimize false positives, prevent missed detections, and accurately segment adjacent particles. Flow rate, sample volume and auto image rate were optimized to maintain the desired calculated imaging efficiency. Subvisible particle size range 5 µm – 100 µm was used.

After parameter optimization, reference images were acquired and archived as libraries.
For each library, statistical filters were generated from particle morphometrics (e.g., area, aspect ratio, circularity, compactness, convexity, diameter, elongation, intensity, symmetry, and transparency). Libraries spanning broad size distributions (5–50 µm) were partitioned into size-binned filters (e.g., small/medium/large) to improve classification performance. Statistical filters were consolidated into classes, and a classification template was generated for automated image classification.



Sample Preparation

Control experiments with nanopure water, indicated that vortex mixing in volumetric flasks generated substantial silicone oil droplets and glass fragments. Accordingly, multiple container types and mixing conditions were evaluated; *vortexing produced increased particle image counts in all containers.*

	Particles/mL (5-50 µm)	3x rinsed	3x rinsed, vortexed	Major classification after vortex
	20 mL Volumetric flask	803	2950	silicone droplets, glass fragments
★	5 mL Polypropylene tube	0	32	silicone droplets, filter material
	50 mL Polypropylene tube	16	632	silicone droplets, plastic
★	20 mL Scintillation vial	4	12	glass fragments, fibers

To ensure reproducibility, samples and controls must be processed under identical handling conditions. Based on control findings, 5 mL polypropylene tubes and 20 mL scintillation vials were selected for sample preparation; containers were triple-rinsed with nanopure water before use, and samples were prepared at 10 % w/w SBECD in water. Samples and controls were prepared without vortexing – only gentle inversion after all solid material was dissolved.

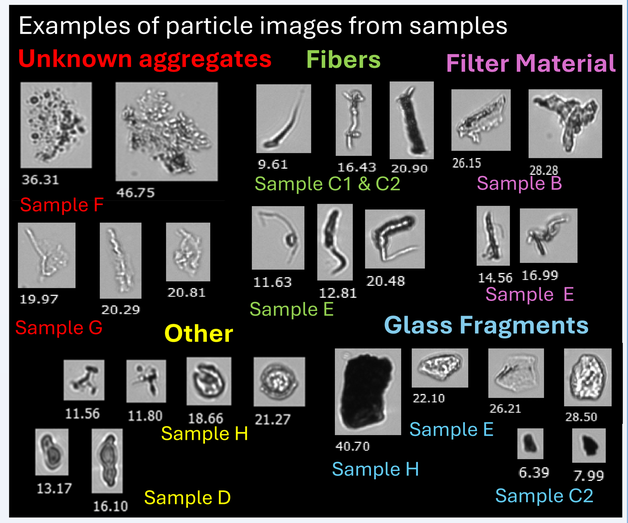
RESULTS

Particle Image Classification -Particles/mL								
Sample	Silicone Droplets	Filter Material	Weigh Paper	Glass Fragments	Unknown Aggregates	Fibers	Plastic	Other
CAPTISOL			12			4		
A	24	20	24		4	4	44	
B	24	40	8		4	16	28	
C1	91	20	28		4	24	36	
C2		219	56	48		40	76	
D	9	20	3	5	37	28	11	
E	310	640	127	119	139	167	131	
F	795	60	60	16	2978	119		223
G	2576	636	107	163	1924	56	243	44
H	5578	3853	751	115	14421	48	159	1555

Sample	Particle Size Distribution - particles/mL			
	Total	5-10 µm	10-25 µm	25-50 µm
CAPTISOL	16	12	4	
A	119	91	6	4
B	119	83	28	8
C1	203	175	28	
C2	437	354	80	4
D	449	414	36	
E	1634	1360	262	12
F	4028	3380	620	28
G	5749	5407	310	32
H	26480	24003	2457	20

Same sample reproducibility ~ 1-3% RSD

Replicate sample reproducibility ~10% RSD



CONCLUSIONS

Using multiple filters per particle class improved automated image classification. Rigorous, matched sample and control preparation was essential for reproducibility. Although the approach does not provide absolute quantitation or definitive particle identification, it enables rapid, image-based screening of particulates relevant to formulation investigations. Marked variability in particle burden and composition across SBECD sources underscores the importance of choosing a reliable excipient supplier.

REFERENCES

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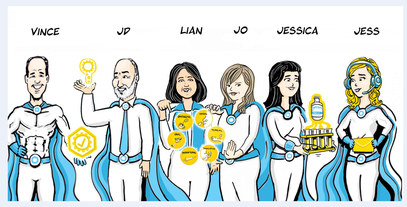
CONTACT



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