5-7-2017

Particulate contamination in single use systems: Measurement challenges

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PARTICULATE CONTAMINATION IN SINGLE-USE SYSTEMS: MEASUREMENT CHALLENGES

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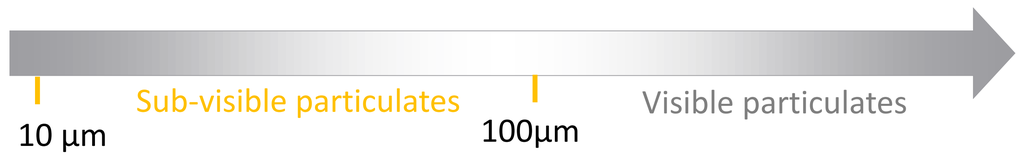
Summary

In the application of single-use systems (SUS), the pharmaceutical manufacturer "outsources" process cleanliness to the manufacturer of the SUS, since no rinsing or cleaning occurs prior to implementation. While visual inspection may detect "visible" (≥ 100 microns) particulate contamination, the probability of detecting particulates on fluid contacting surfaces within single-use components remains low due to the difficulty of seeing through translucent or turbid plastics. Extraction (flushing, washing) of fluid contact surfaces allows collection of particles for quantitative microscopic analysis. Here we present studies comparing extraction methods (agitation/rinsing), and extraction fluids (solvents/aqueous media). These studies highlight challenges in the development of methods for measurement of particulate contamination in SUS.

Definitions and Methodology

Visible Particulates (particles and/or fibers)	≥ 100µm
Sub-visible Particulates	10-100µm

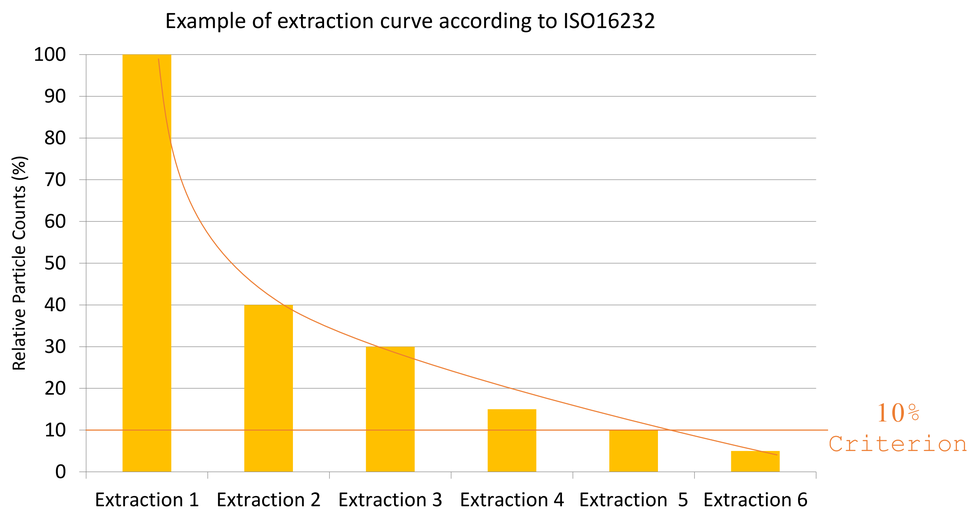


ISO 16232 (VDA 19) determination of extraction efficiency:
- Repeated extraction of same component under constant conditions
- Calculate relative particle counts (%):

$$\frac{C_n}{\sum_{i=1}^{n} C_i} \times 100$$

C, cleanliness value
n, the number of the extraction, $6 \geq n \geq 1$

Extraction is efficient if 10% achieved within 6 extractions

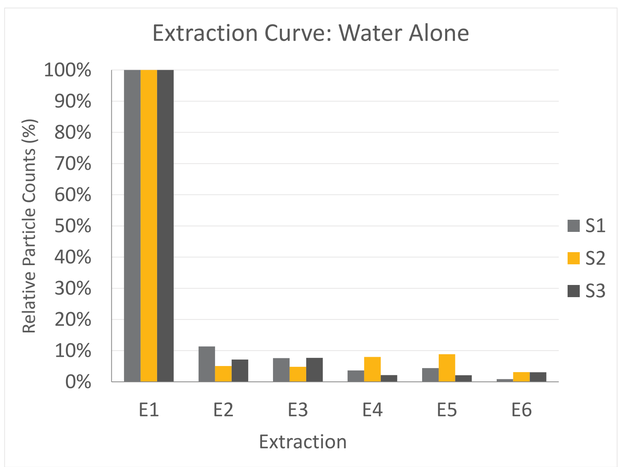


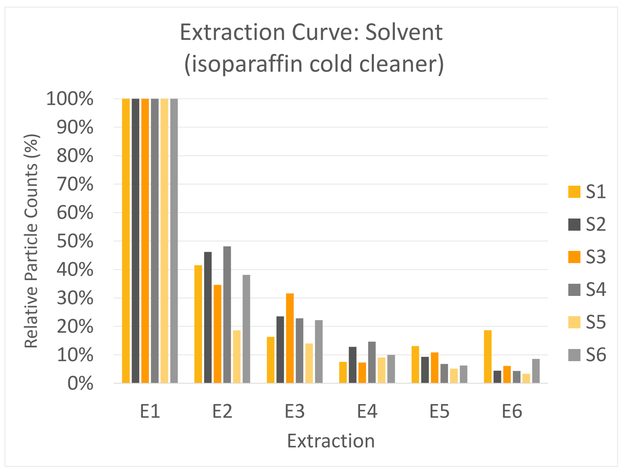
Test System: Single-Use Bags

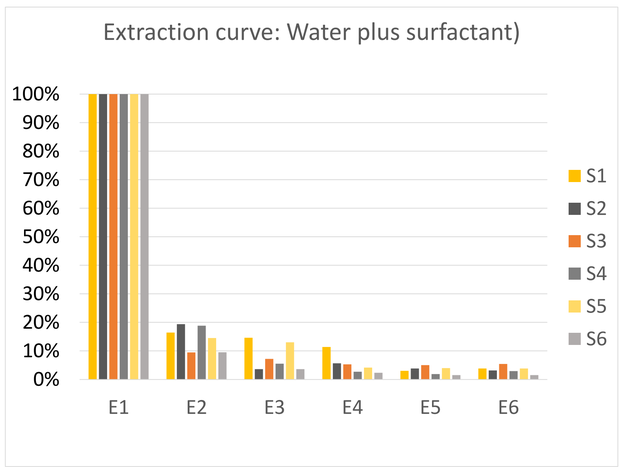
Extraction critical parameters:
- extraction fluid (solvent/water/water plus surfactant)
- agitation (intensity, liquid volume): fill bag with liquid, controlled rocking, drain
- rinsing (flow rate, liquid volume): flush bag with liquid, controlled flowrate

Extracted liquid containing extracted particulates is filtered onto membrane
Visible particulates counted and sized using automated microscopy

Effect of Extraction Fluid (agitation/rinsing held constant)



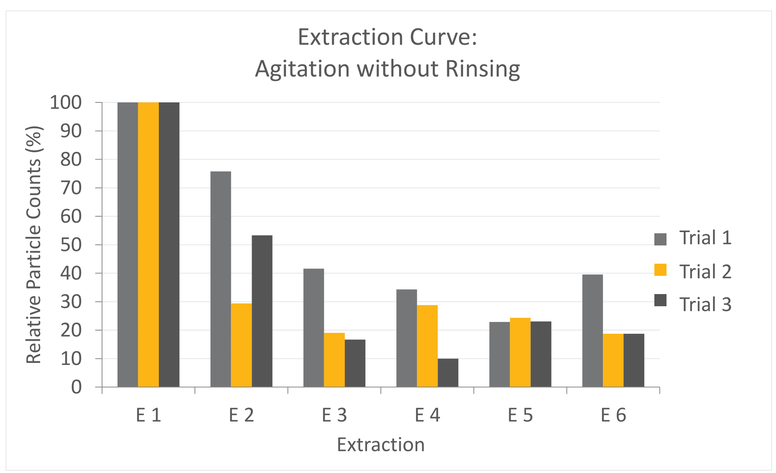


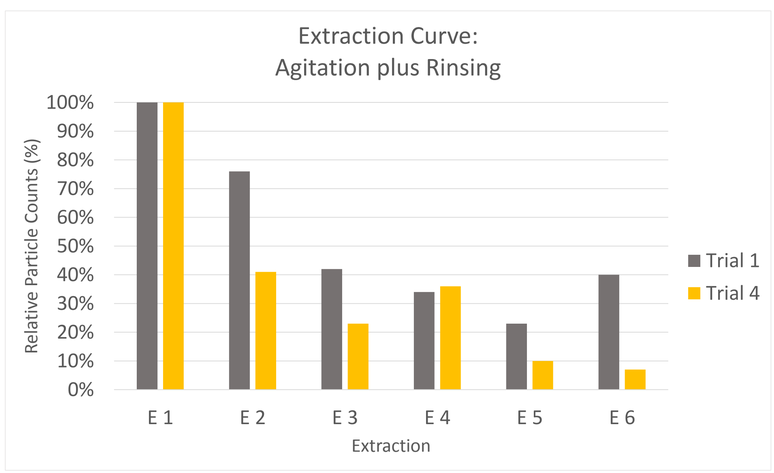


For this extraction method:
All solvents achieve 10-20% criterion within 6 extraction steps

All solvents result in efficient extraction within 6 extraction steps

Effect of Extraction Conditions (extraction fluid held constant)





For these tested bags:
Agitation alone is generally not sufficient for 10-20% criterion

Agitation plus rinsing is efficient

Trial 1: Fill with 2x volume, agitation 2x
Trial 2: Fill with 1x volume, agitation 2x
Trial 3: Fill with 1x volume, agitation 1x, rest 1min, agitation 1x

Trial 4: Filling with 2x volume, agitation 2x, rinsing with 1x volume

Identification

We apply optical microscopy (polarized light), infrared microscopy along with electron microscopy for the identification of particulates:

Conclusions

Challenges arise in development and validation of methods for extraction of particulate contamination within the interior of single-use bags. The complex geometries of single-use bags often hinders easy removal of particulates, and a combination of agitation and rinsing may be required. *Under the specific agitation/rinsing conditions and for the specific types of single-use bags studied here,* efficient extraction is achieved with water alone, solvent, or water plus surfactant according to ISO 16232. Particle counting and sizing is only the first step in the particle analysis process: particle identification, source identification and design optimization are required for guiding improvements in cleanroom processes and operations.

Acknowledgements

The authors thank Manon Thaüst and Véronique Cantin for their contributions to this work.