Welcome to Particlese

One must explore deep and believe the incredible to find the new particles of truth floating in an ocean of insignificance.

- Joseph Conrad

Particlese (pahr-ti-kleez)

What is Particlese?

Who we are

- Particlese
  - Consulting practice specializing in pharmaceutical particle and spectroscopic challenges
  - Knowledgeable partner for the commercial science community
- Kevin Dahl, Ph.D.
  - Experienced spectroscopist and particle characterization professional
  - 15+ years of commercial experience in particles
  - 25+ years of academic/commercial experience in spectroscopy
  - Deep R&D background in pharmaceutical analytics
  - Associate Director/Director of commercial specialty particle team
  - Five years experience managing GMP laboratory
  - Author of numerous SOPs and Methods for use in GMP analyses

Particlese: Expertise

- Enumeration
  - Visual Inspection
  - Light Obscuration
  - Flow Microscopy
  - Static Microscopy
- Particle Characterization
  - Optical Microscopy/PLM
  - Raman/FTIR Microspectroscopy
  - SEM-EDS
- Other
  - Spectral Interpretation
    - Theory and Practice
  - Bulk Raman/FTIR Spectroscopy
  - Laser Diffraction
  - Dynamic Light Scattering
  - Nanoparticle Tracking Analysis
  - Imaging Flow Cytometry
  - Fluorescence Microscopy
  - NIR Imaging

Particlese: Consulting and Service Offerings

- Method Consulting
  - Development, Optimization, Qualification, Validation
- Experimental Consulting and Services
  - Study design, execution, analysis, interpretation
- Data Consulting
  - Reanalysis, interpretation
- Document Consulting
  - Drafting and Review
  - R&D and GMP
- Training Services
  - Selected Instruments

Particlese

Service Examples

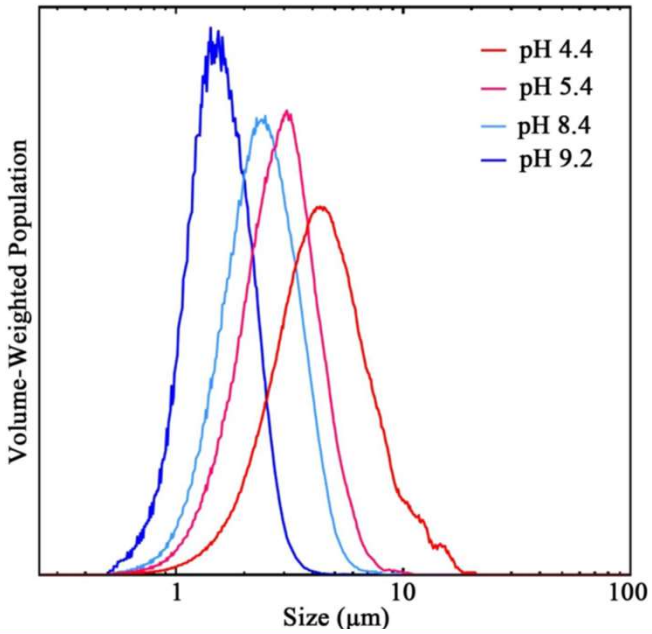
Method Consulting

Method: Neat Topical Method Development

- Topical products present a unique analytical challenge
  - Semi-solid with high globule population necessitates dilution for traditional techniques (LD)
  - Effects of dilution on the globule size distribution are unknown
    - Adulteration, coalescence, etc.
- Manual optical microscopy has been used to examine cream product homogeneity
  - Statistically low-power technique
- Automation of optical microscopy provides statistical description of sample
  - High globule population requires modified optical settings to improve contrast of globules for proper (software) separation

Sutton, M.J., Osborne, D.W., Dahl, K., Bax, V. and Schick, G.A. (2018). Characterization of a Liquid Crystal Stabilized Pharmaceutical Oil-in-Water Emulsion Optimized for Skin Delivery. Journal of Cosmetics, Dermatological Sciences and Applications, 8, 207-217.

Method: Neat Topical Method Development



pH of Cream	D_V10 (µm)	D_V50 (µm)	D_V90 (µm)
4.4	2.3	4.3	8.2
5.4	1.6	2.8	4.5
8.4	1.4	2.3	3.7
9.2	1.0	1.5	2.3

- Automated optical method shows pH dependence of globule size for Crodafos cream
  - Stabilization of the globules improves as pH increases
  - Mixing speed constant during experiments
  - Neutralization of emulsifier chemistry likely drives globule formation and stability
- Rapid, statistical measure of globule size
  - Monitor stability
  - Observation of coalescence

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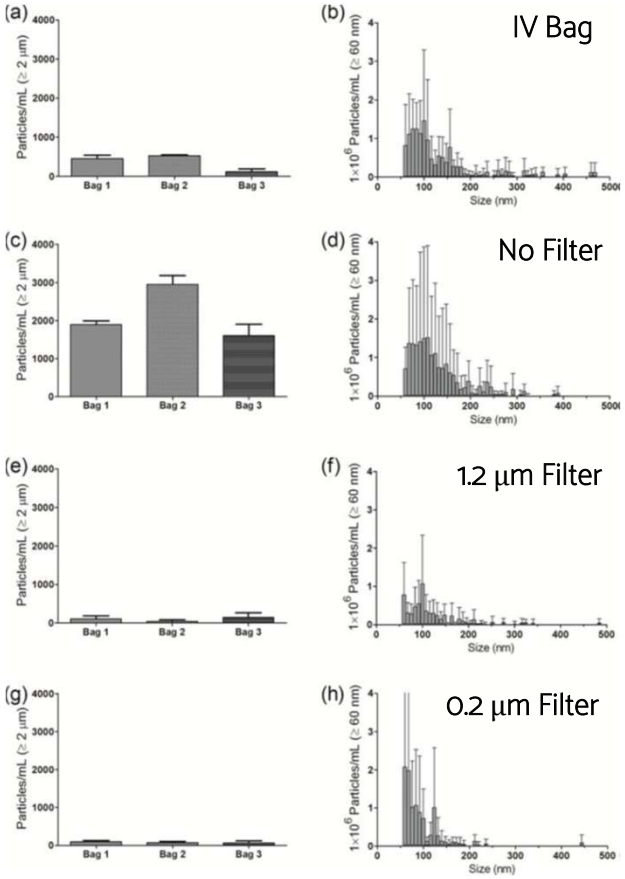
Experimental Consulting and Services

Study: Filter Effectiveness During IV Infusion

- Effectiveness of in-line filters to remove particulates during simulated IVIG infusion
  - Micro- and nano-particle population and particle characterization
  - Techniques: FM, NTA, Raman Microspectroscopy (RMS)
- Pre-filled saline bags with in-line filters
  - Control saline (Baxter and Hospira)
  - Gammagard® (Baxter) at 0.4 mg/mL
  - In-line Filters (1.2 μm CareFusion, 1.2 μm Baxter, 0.22 μm Baxter)
  - Pumped at 140 mL/hr

Pardeshi, N. N., Qi, W., Dahl, K., Caplan, L., & Carpenter, J. F. (2017). Microparticles and Nanoparticles Delivered in Intravenous Saline and in an Intravenous Solution of a Therapeutic Antibody Product. Journal of Pharmaceutical Sciences, 106(2), 511–520.

Study: Filter Effectiveness During IV Infusion



- Infusion of saline
- Microparticle population increases significantly after infusion without filter
  - Represents debris from contact surfaces
- Incorporation of filters significantly reduces debris population
  - Microparticle population is nearly eliminated
  - Nanoparticle population relatively stable with reduction in nanoparticle population greater than 0.2 µm with 0.2 µm filter

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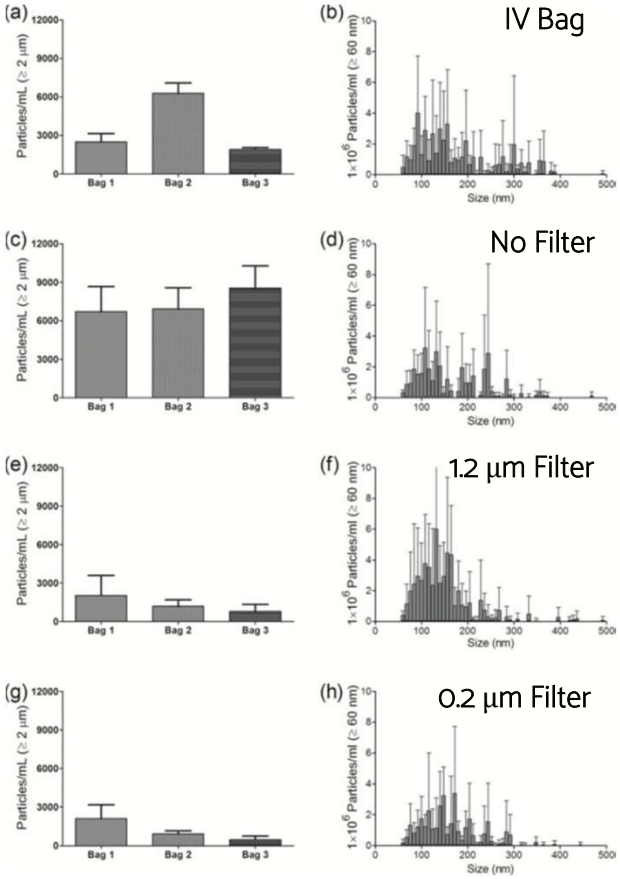

- Infusion of IVIG
- Microparticle population increases significantly after infusion without filter
  - Represents debris from contact surfaces plus aggregates formed on contact surfaces sloughing off
- Incorporation of filters significantly reduces debris population
  - Microparticle population is not eliminated
    - Post-filter aggregates?
  - Nanoparticle population relatively stable across all samples

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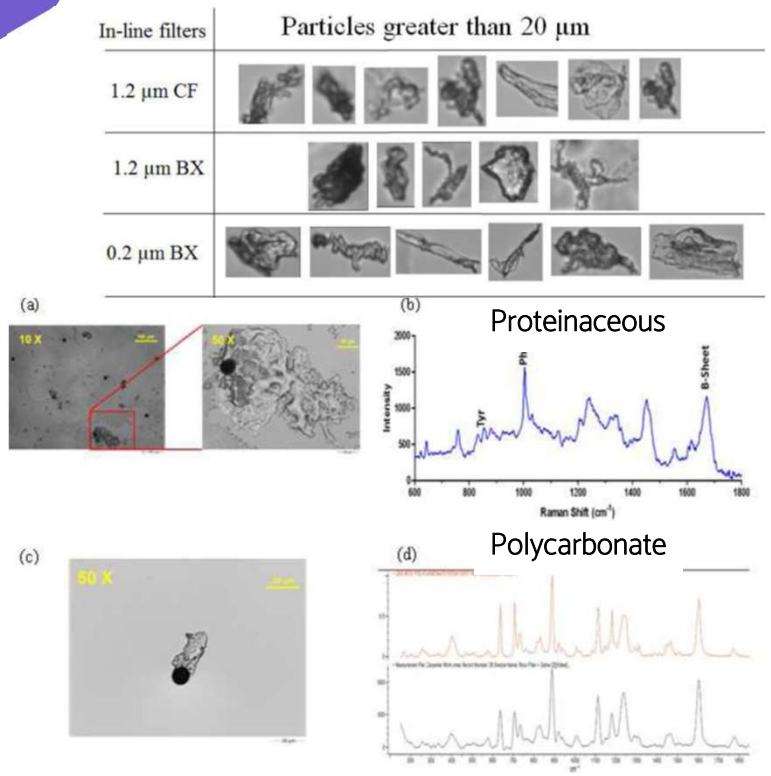

- Significant particle population is observed ABOVE 20 µm post-filter (0.2 µm Baxter)
  - Identification using Raman microspectroscopy (RMS)
  - Particles captured on novel fused silica membrane
- Large (>50 µm), gelatinous bodies
  - Identified as proteinaceous aggregates
- Small, transparent bodies
  - Identified as polymeric
  - Likely from Luer adapters
- Additional fluorescence labeling showed the deposition of hydrophobic IVIG to contact (polymer) surfaces during infusion

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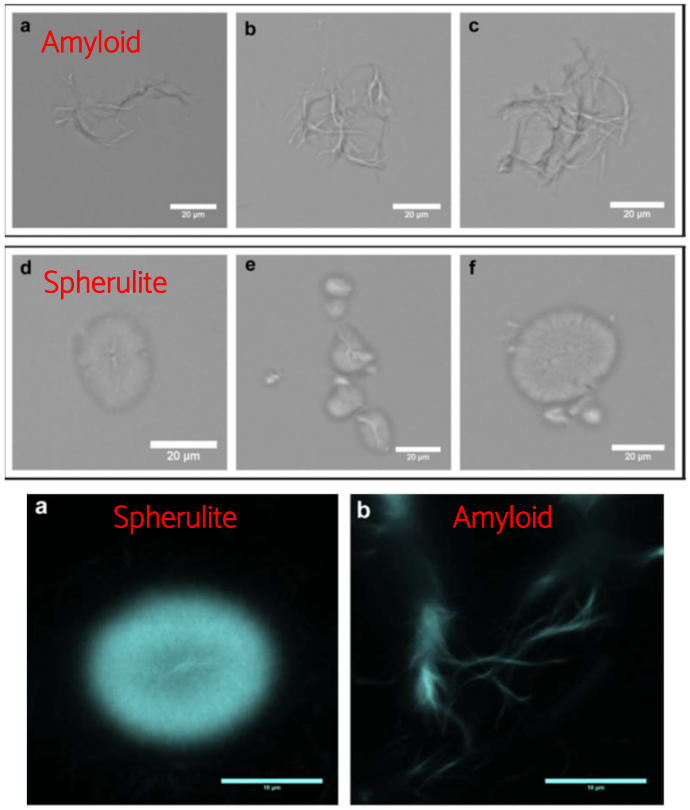
Data Consulting

Research: Spectroscopy of Aggregates

- Goal: determine if morphological differences in proteinaceous aggregate types are also expressed in their vibrational spectra
  - Aggregate formation is controlled by environment and can lead to morphologically-distinct populations
- Are 2° or 3° structural differences observed in the Raman spectra
  - Raman spectral changes due to protein structural changes are well understood

Schack M.M., Dahl K., Rades T., Groenning M., Carpenter J.F. (2019). Spectroscopic Evidence of Tertiary Structural Differences Between Insulin Molecules in Fibrils. Journal of Pharmaceutical Sciences, 108(9), 2871-2879.

Research: Spectroscopy of Aggregates



- Two types of aggregates of human insulin prepared
  - (1) 1 mg/mL in acetic acid (pH 1.95)
  - (2) 1 mg/mL in HCl (pH 1.85)
  - 45 °C for 16 hr
- Particles captured by centrifugation on calcium fluoride flats
  - Aggregates labeled with thioflavin T (fibril/amyloid sensitive)
- Significant morphological differences
  - Population (1) – amyloid
  - Population (2) - spherulite
- Thioflavin T fluorescence observed in both populations

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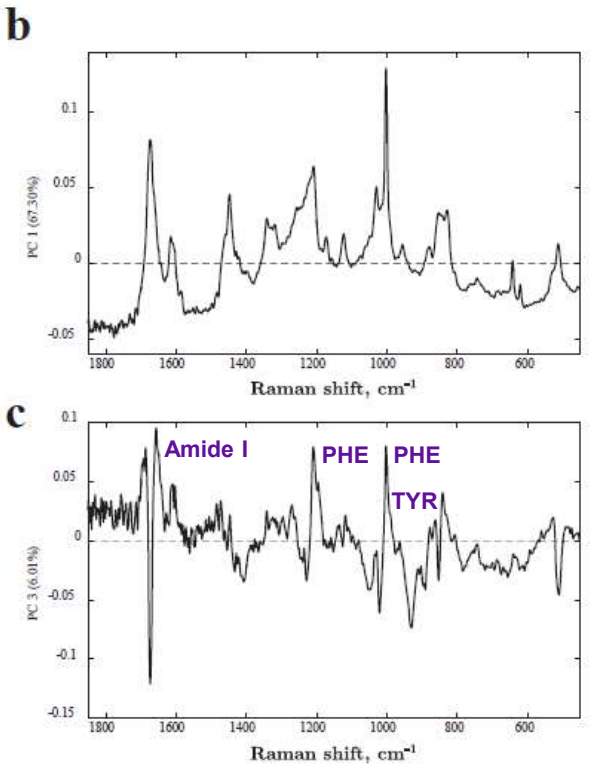

- Spectra compared using PCA
  - Spectra are grouped based on variance in the spectrum from the spectral average
- Loading One (b) describes the average of the spectral data set (amyloid)
- Loading Three (c) describes changes from the average for spherulite aggregates
  - More hydrophobic environment
  - Increased particle density
- Observations are consistent with the morphological differences between the aggregate populations
- Single-particle Raman spectroscopy is sensitive to aggregate structural changes

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Particlese: Consulting and Service Summary

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  - Clark Frye
- Method Consulting
  - Development, Optimization, Qualification, Validation
- Experimental Consulting and Services
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