



2019 PDA Visual Inspection Forum

Preparing for the Future of Visual Inspection



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REGULATION®

APRIL 23-24 | WASHINGTON, DC

EXHIBITION: APRIL 23-24

AN INTRODUCTION TO VISUAL INSPECTION TRAINING COURSE: APRIL 25-26

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#PDAVisual

Utilization of a Forensic Microscopy (Problem Solving) Approach to the Identification of Subvisible Particles Observed in a Sterile Ophthalmic Solution on Stability

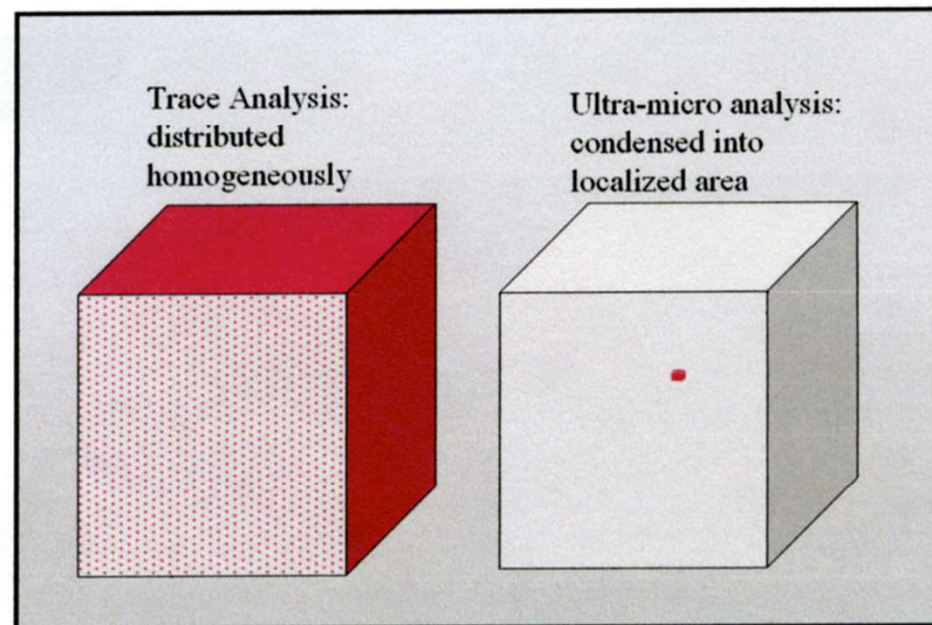
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Outline

- **Sub-Visible Particle ID: Often a trace analysis challenge**
- **Classification of particle types and compendial expectations**
- **Example: Identification of sub-visible particulates formed during stability and particle source**

Particle Characterization = Ultra-Microanalysis



Pharmaceutical Particle Classification

Extrinsic

- Hairs
- Celluloses
- Skin Flakes
- Fibers, Lint
- Insect parts
- Glass
- Soil
- Cleanliness of pkg components

Intrinsic

- Formulation ingredients
- Packaging component related
 - Si oil, slip agents, shavings
- Changes on stability
 - product/pkg interaction
 - precipitation of actives or inactives
- Particle generation during filling process

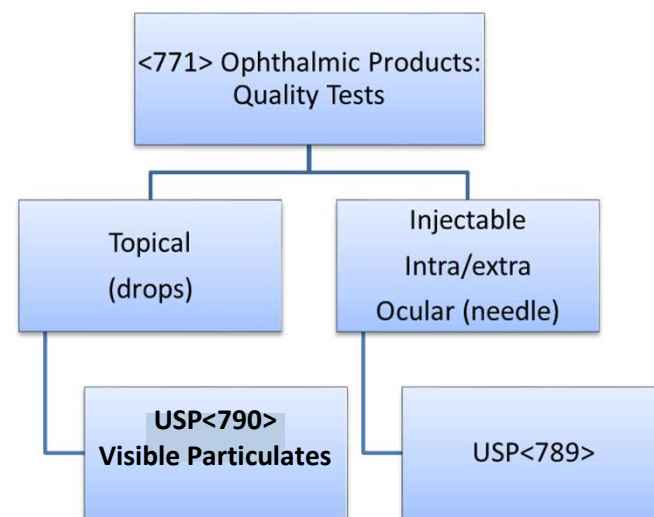
Inherent

- Protein aggregates

Particle Requirements for Parenterals and Ophthalmic Solutions (injectables vs topical drops)

New content:

Visible inspection of cell and gene products
Silicone oil droplets and impact on subvisible particle counts in biopharmaceuticals



Particle Morphology and Estimate of Single Particle Mass

Needle Morphology: $100 \times 2 \times 2 \mu\text{m}$

Volume: $400 \mu\text{m}^3$

Mass/particle:

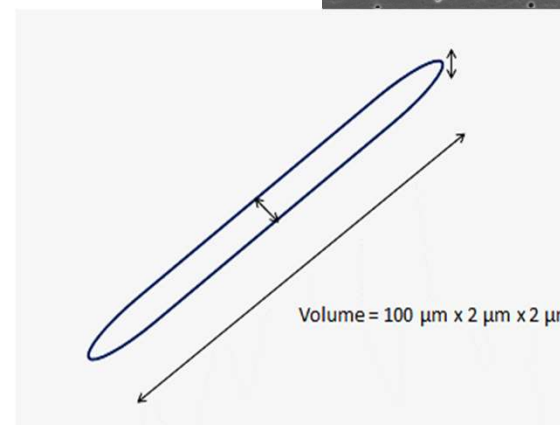
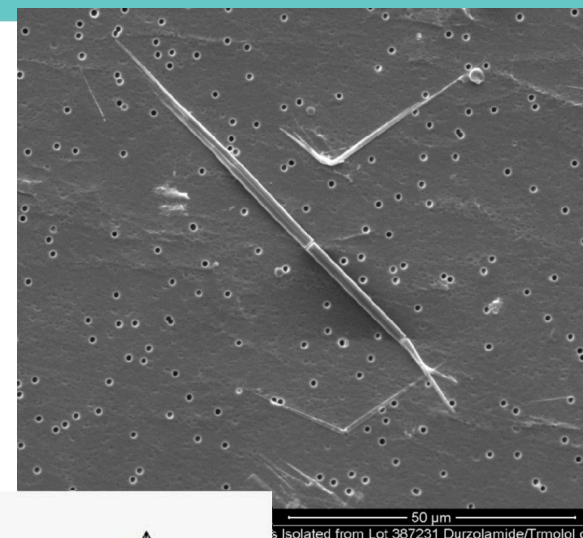
$(400 \mu\text{m}^3) * (10^{-4} \text{ cm}/\mu\text{m})^3 * 1.5 \text{ g}/\text{cm}^3$ (density)

$= 6 \times 10^{-10} \text{ g/particle}$ or 0.6 ng/particle

At the USP<789> limit of 50 particles/mL

$\approx 30 \text{ ppb}$ in single bottle!

Thousands of Particles Correlates to
Low ppb Concentration!

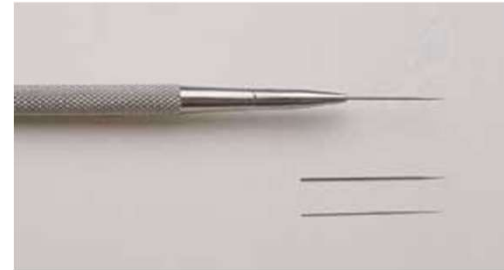


Direct, Physical Removal of Specimen from the Matrix

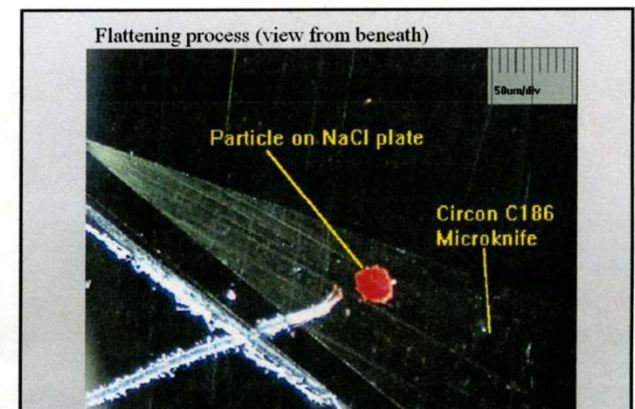
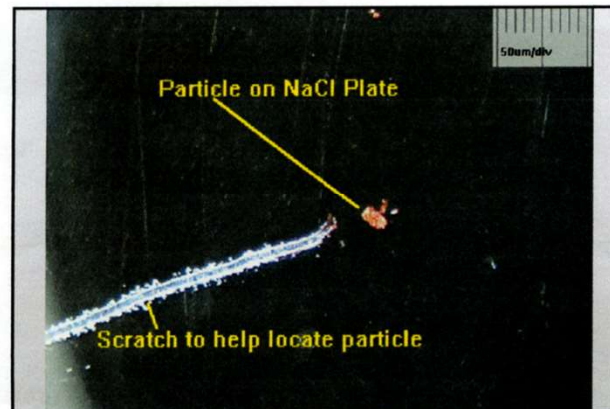
Direct removal, dry: tungsten needle,
MicroTools

Direct removal, wet: capillary tube
(Wiretrol)

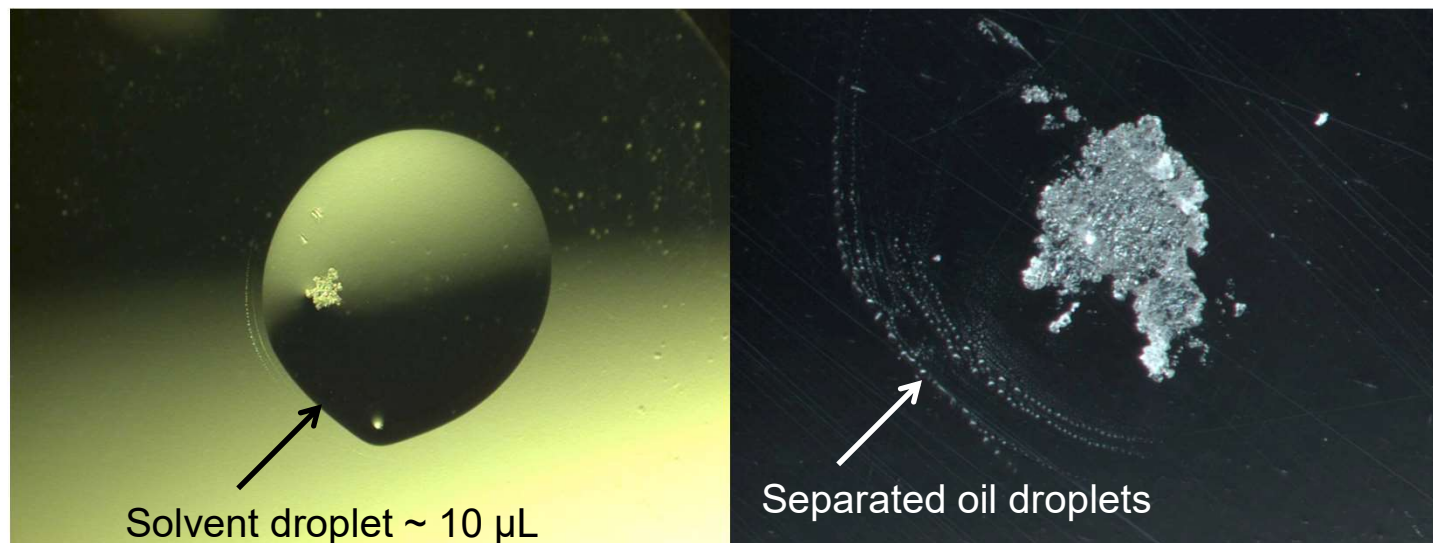
Class 100 Clean Hood: Handling, Filtration



Negative Controls Essential!



Serial Solvent Washing: Multicomponent Sample



What extracts, separates?
Solubility of components in various solvents
Non-polar $\longrightarrow$ Polar

Forensic Microscopy: Sequential and Progressive Particle Characterization Approach

Visual Inspection and Low Power Stereomicroscopic Examination
(understanding the appearance & context of the specimen)
Physical Tests: Pressing (elastomeric, brittle); Magneticty



Polarized Light Microscopic Examination
(size, shape, color, crystallinity)



Thermal Analysis: Flame Test and/or Hot Stage Microscopy
(Is it organic, inorganic or mixture?)



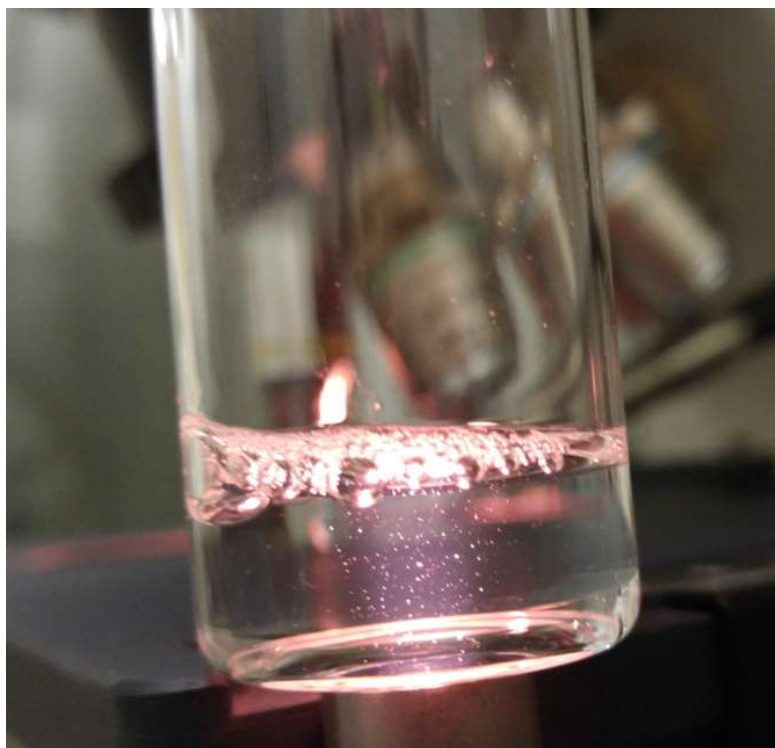
Inorganics: Microchemical tests, Refractive index, SEM-EDS
Organics: IR microscopy (size limit ~ 15-20µm) , Raman microscopy (to ~ 1 µm),
Atmospheric Solids Analysis Probe MS

Sterile Ophthalmic Solution

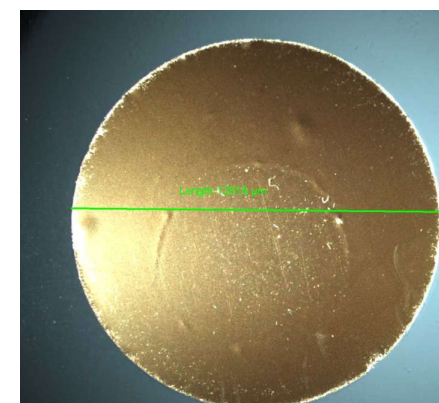
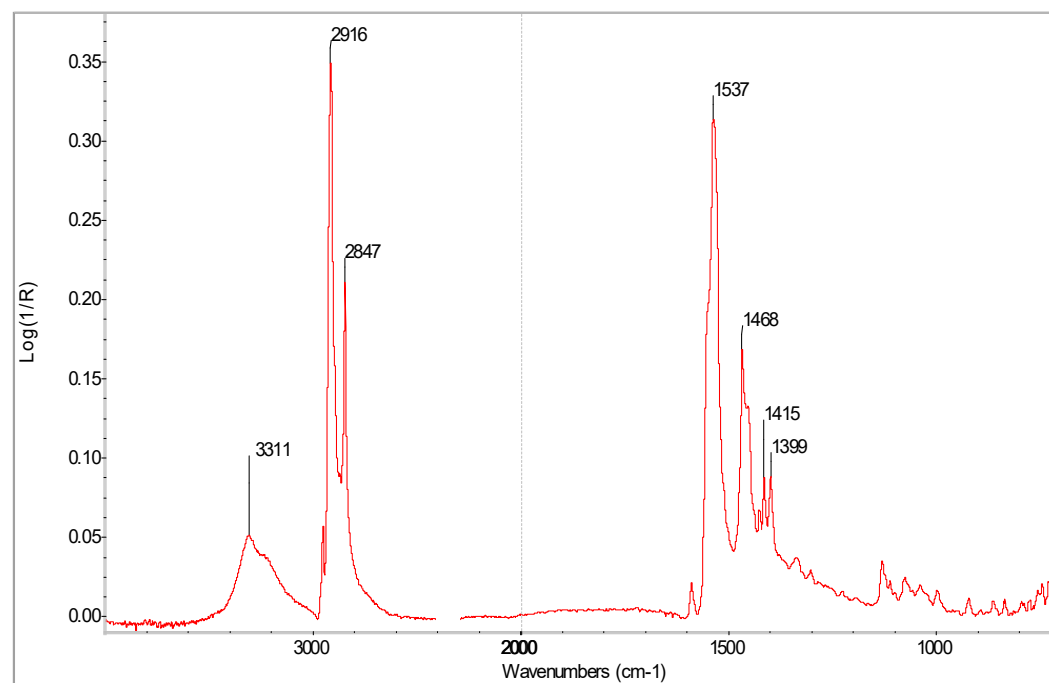
Travoprost 0.004% ophthalmic solution
Prostaglandin analog; treatment for glaucoma

Ingredient	Source or grade	Each mL contains (mg)	Function
Travoprost	Industriale Chimica/USP	0.040	Drug active
PEG-40 hydrogenated castor oil	BASF Chemicals/USP–NF	5.00	Drug solubilizer
Sorbitol	NF grade	2.50	Tonicity
Boric acid	NF grade	10.00	Preservative/buffer
Propylene glycol	NF grade	7.50	Preservative; tonicity
Zinc chloride (ZnCl)	EMD Chemicals/USP	0.025	Preservative
Hydrochloric acid (HCl) and/or sodium hydroxide (NaOH)		q.s. to pH	pH adjustment
Purified water		q.s. to 1 mL	Vehicle

Visible Particle Observation and Particle Morphology

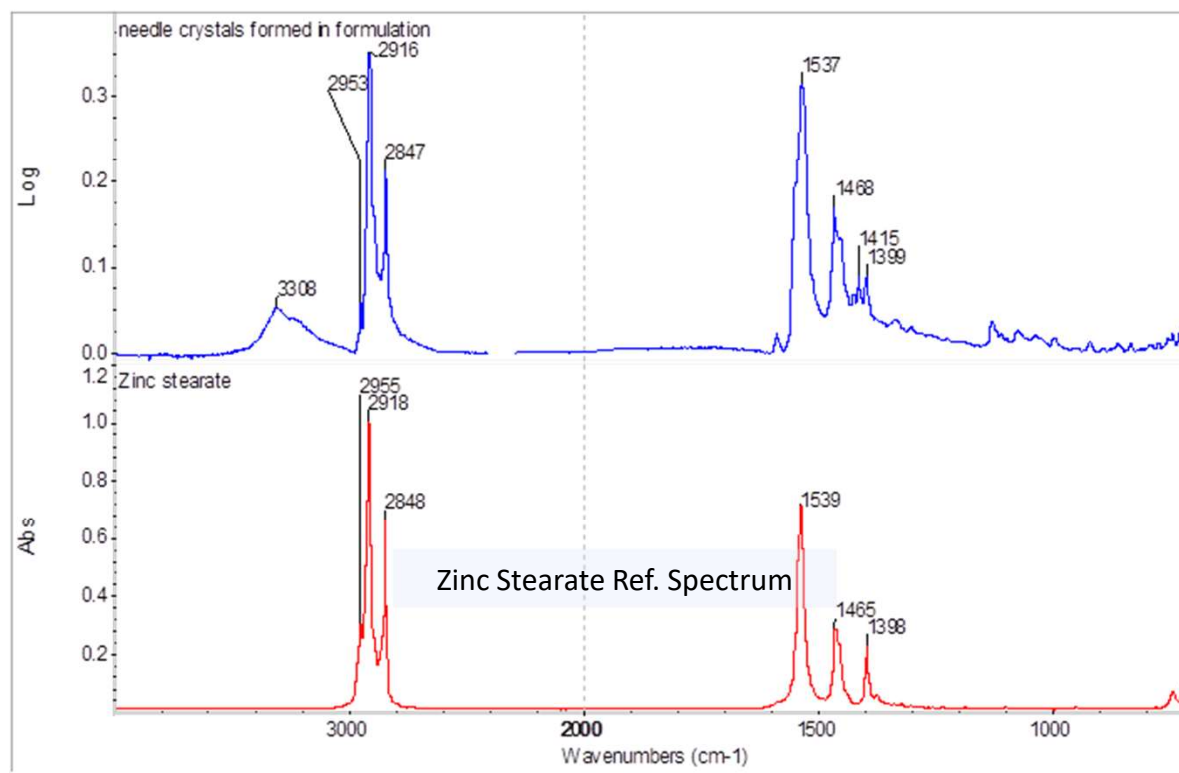


Infrared spectrum (reflectance) of needle particles isolated from ophthalmic solution formulation

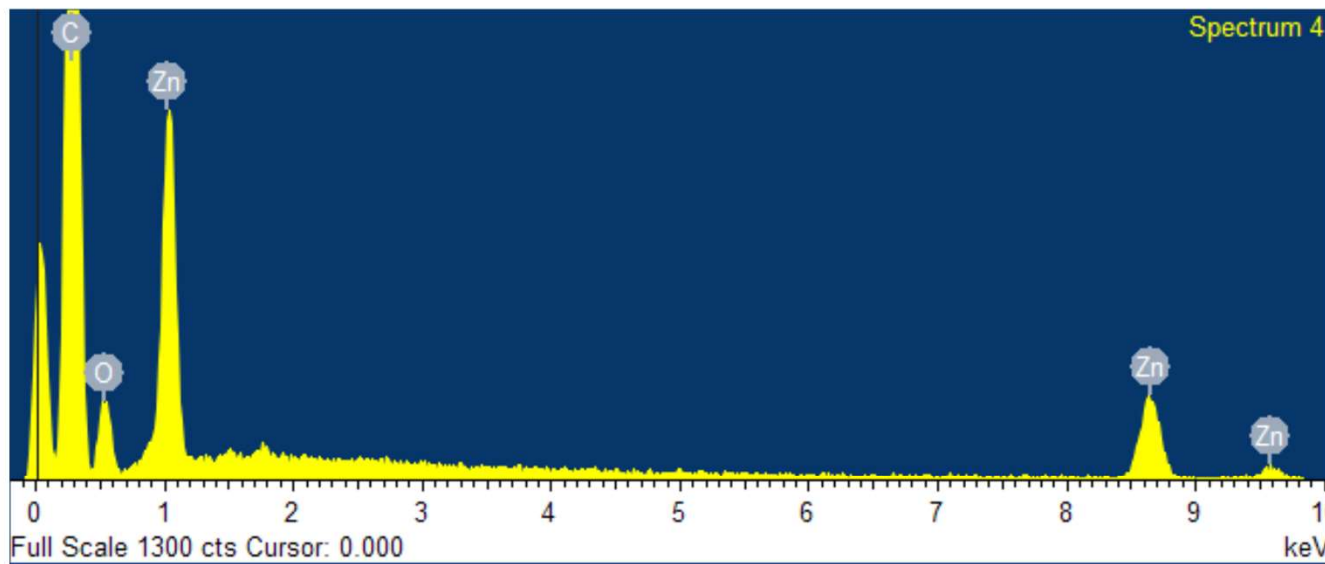


**13 mm gold coated
track etched
polycarbonate**

Infrared Spectral Features Consistent with a Long Chain Fatty Acid Salt



SEM-EDS Spectrum of Washed Particle Isolate



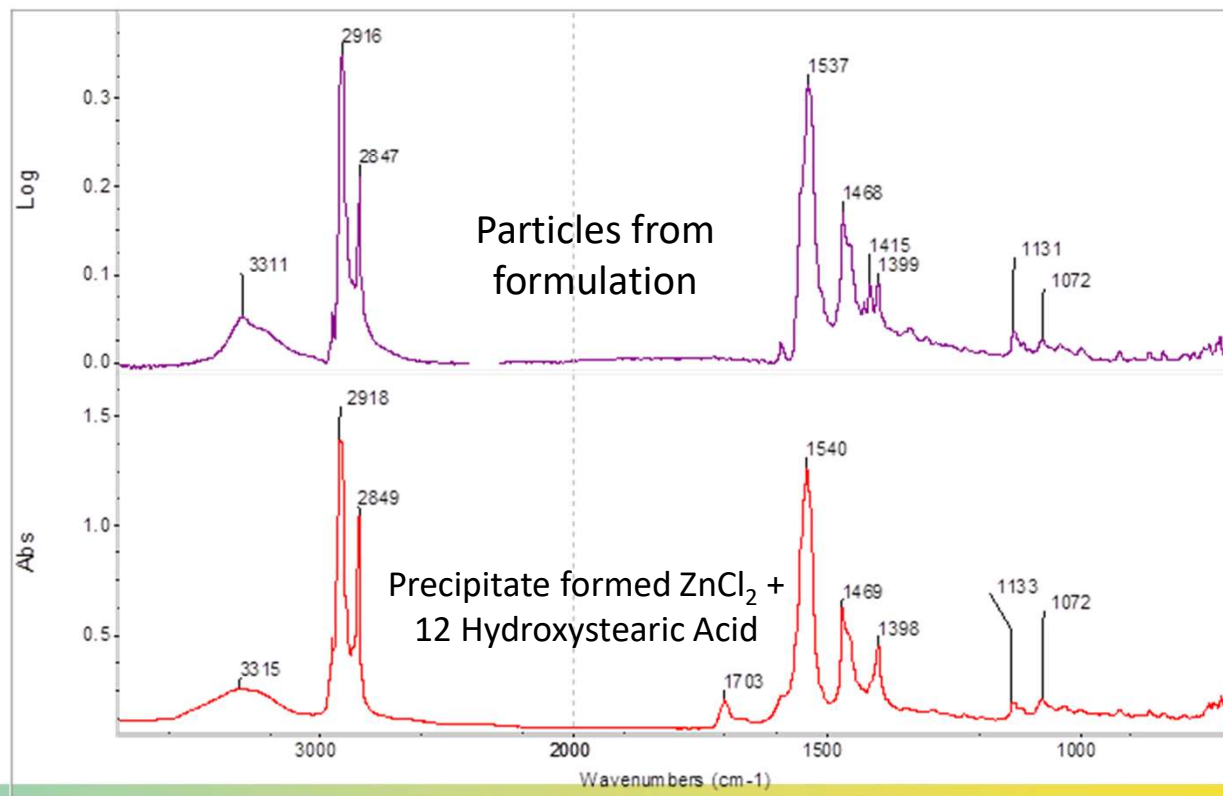
CCCCC[C@H](O)C/C=C\CCCCCCCC(=O)O

Chemical reaction scheme showing the hydrolysis of a polyurethane. A polyurethane chain with three repeating units $(OC_2H_5)_{40}$ is shown reacting with H_2O . The reaction arrow points down to the products: three long-chain diols (each with a terminal OH group) and three long-chain diamines (each with a terminal HO group).

- HSA also potential impurity in the raw material

Verification of Identity

ZnCl_2 at ~ 0.1 mg/mL in water pH ~ 3 + 22 mg/mL HSA in IPA (20 mLs)



Conclusions

- **Problem solving approach follows a simple to complex analytical progression**
- **Maximize data from a minimum amount of sample; attempt to be non-destructive**
- **Progressive data gathering builds a body of evidence to support identity**
- **Goal: Clean & Stable**

Acknowledgments

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