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Identification of Glass Delamination Products Using TEM

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Outline

- Glass delamination background
- Established characterization methodology
- Advantages of TEM
- Examples
  - Delamination flakes
  - Other particle types
  - Secondary products
- Conclusions

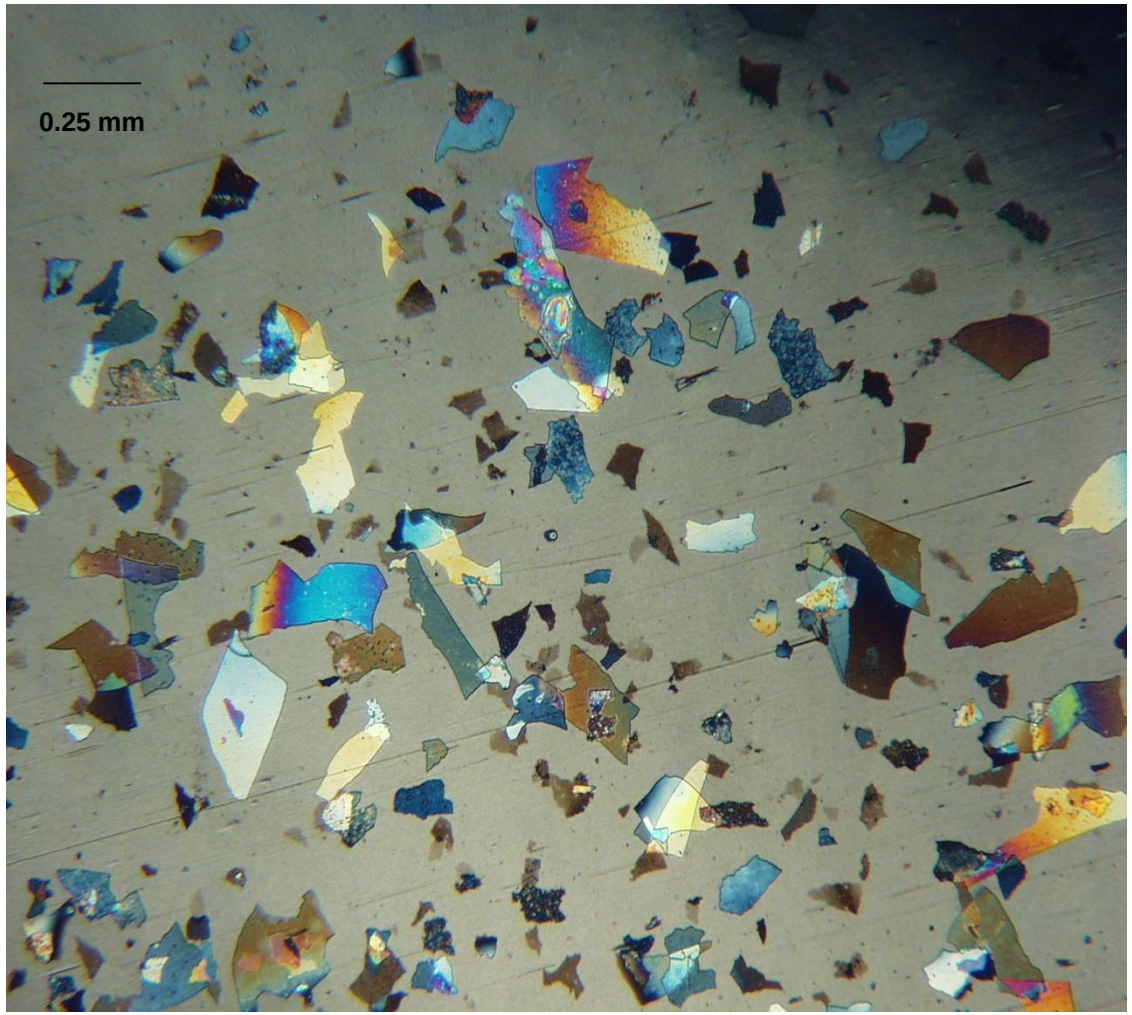
Glass Delamination Background

- **Formation and separation of glass flakes from surface**
  - Last stage indicator of heavy extraction of glass by product
- **Severity of delamination depends upon:**
  - Glass composition, manufacturing method
  - Presence of defects
  - Handling, sterilization
  - Product interactions (pH, buffers)
  - Storage conditions (time, temperature)
- **Risk of particulate in injectables and parenterals in vials**
  - Potential to affect large amounts of product
- **Subject of recent recalls**

Methodology (USP<1660>)

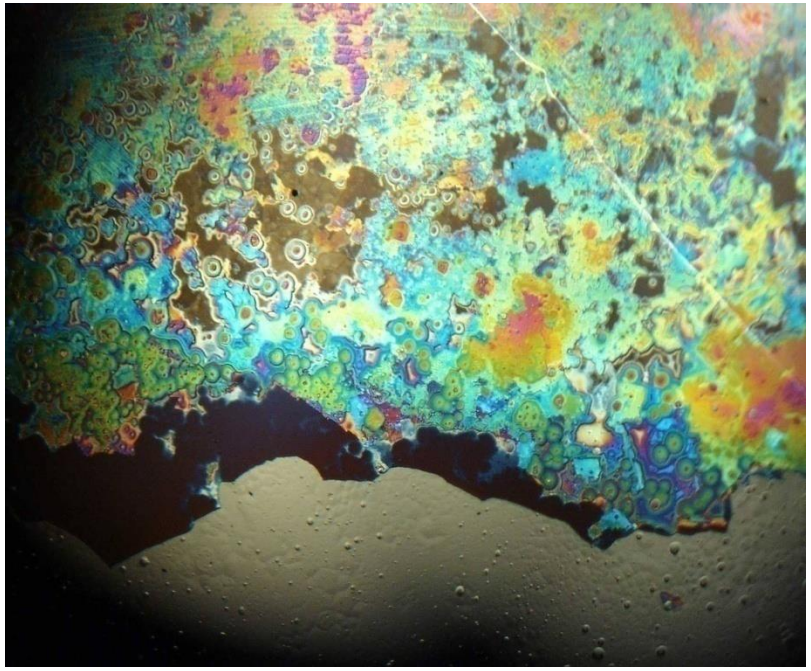
- **Examination as received, visually and using a stereomicroscope**
- **Sample preparation**
  - Filtration of flakes and residues
  - Breaking of taped vials to maintain spatial relationship of vial fragments
- **Characterization using multiple techniques**
  - PLM
  - SEM/EDS
  - FTIR
  - XPS

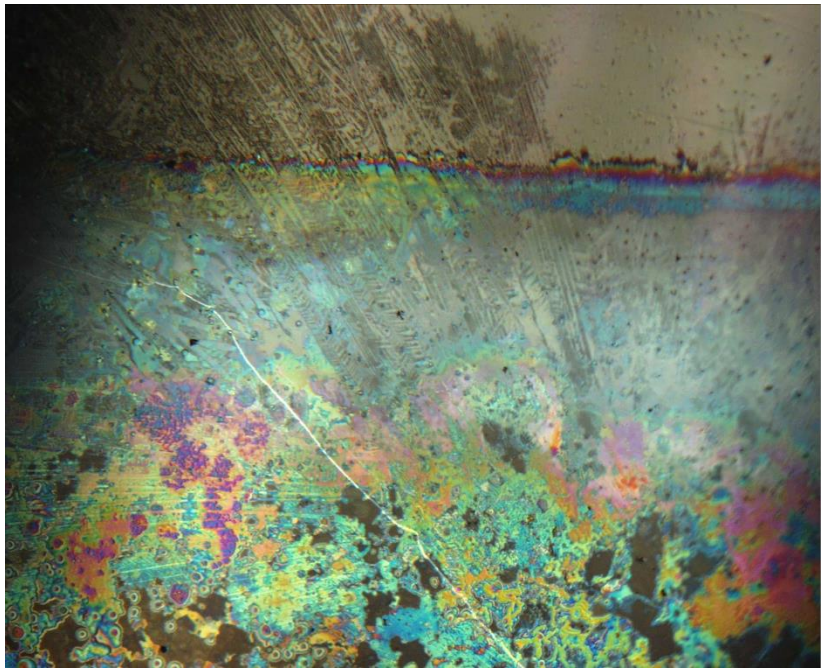
Glass Delamination Flakes on Filter



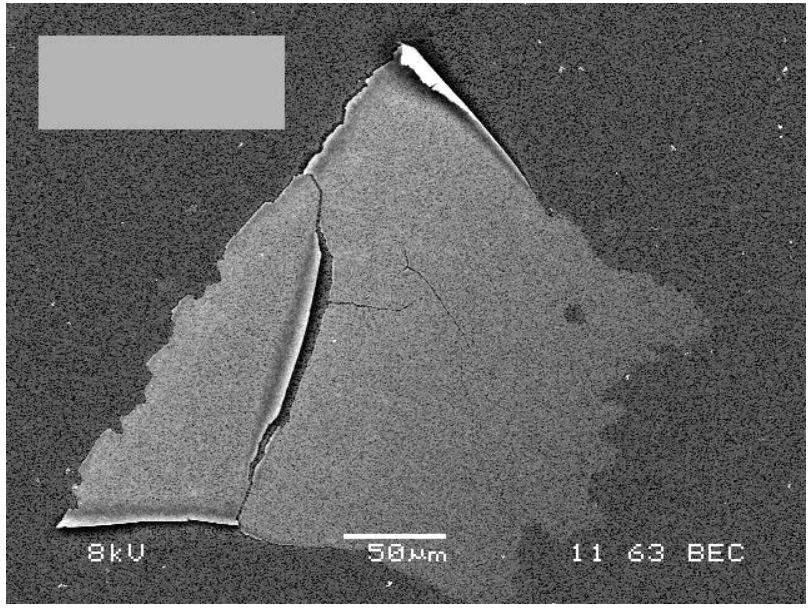
Coaxial Illumination at 50X Magnification

Severe Glass Delamination – Vial Surface

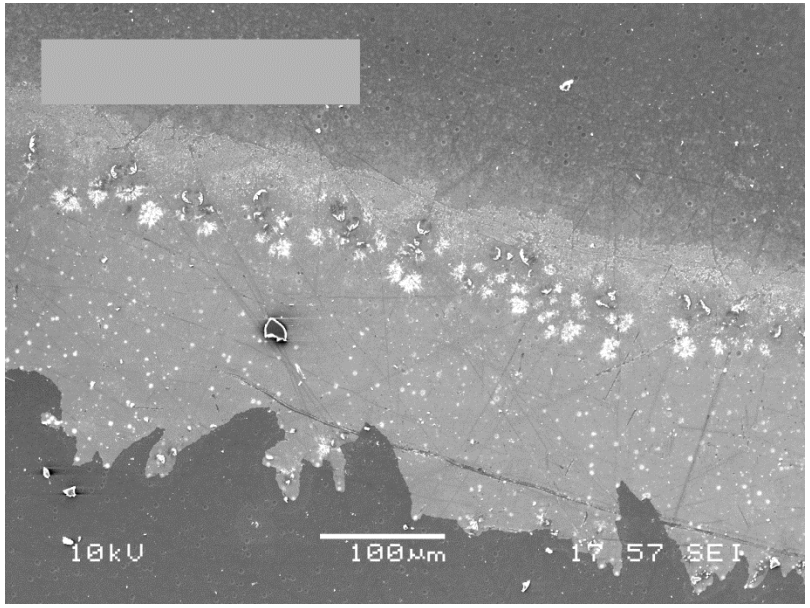




SEM Analysis of Glass Delamination



Flake on filter



Vial surface

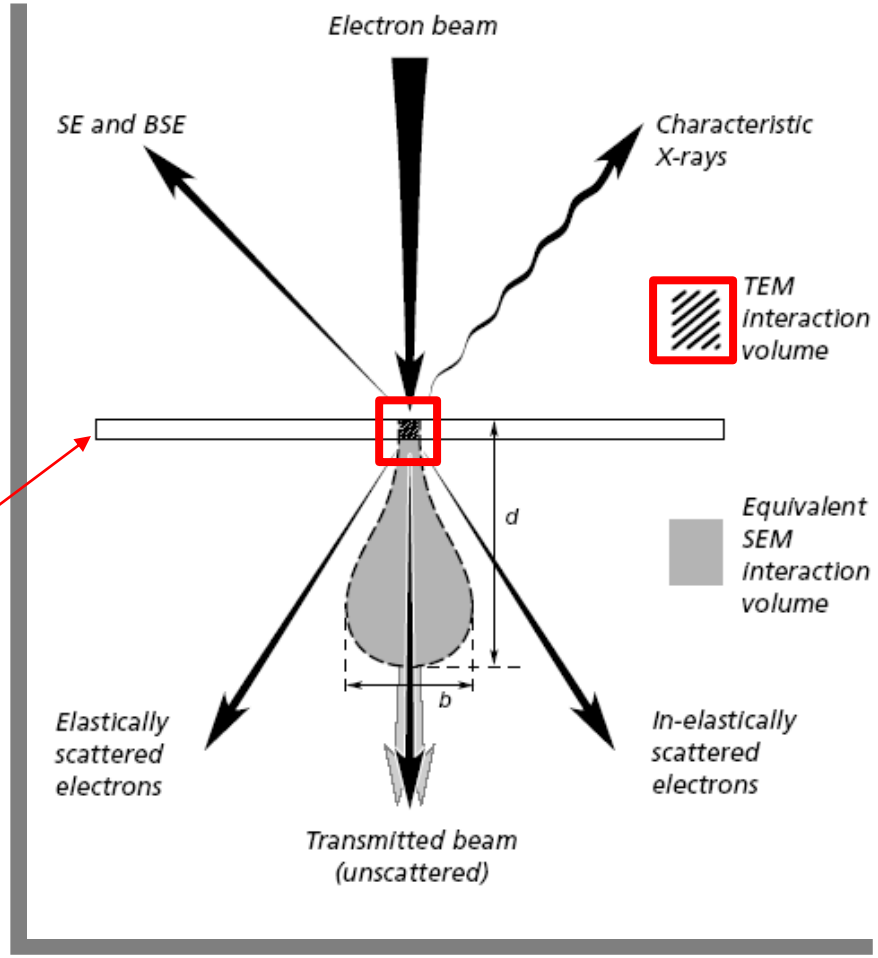
Advantages of TEM

- High resolution, through-sample analysis provides morphological, elemental and crystallographic information.
- Scrapings from vials, delamination flakes and residues are ideal samples, easily transferable to TEM grids.
- TEM/EDS is better suited to very thin samples than SEM/EDS.

TEM and SEM Interaction Volumes

A very low accelerating voltage must be used in the SEM to limit beam penetration through a thin sample.

Sample thickness ~ 90-100 nm



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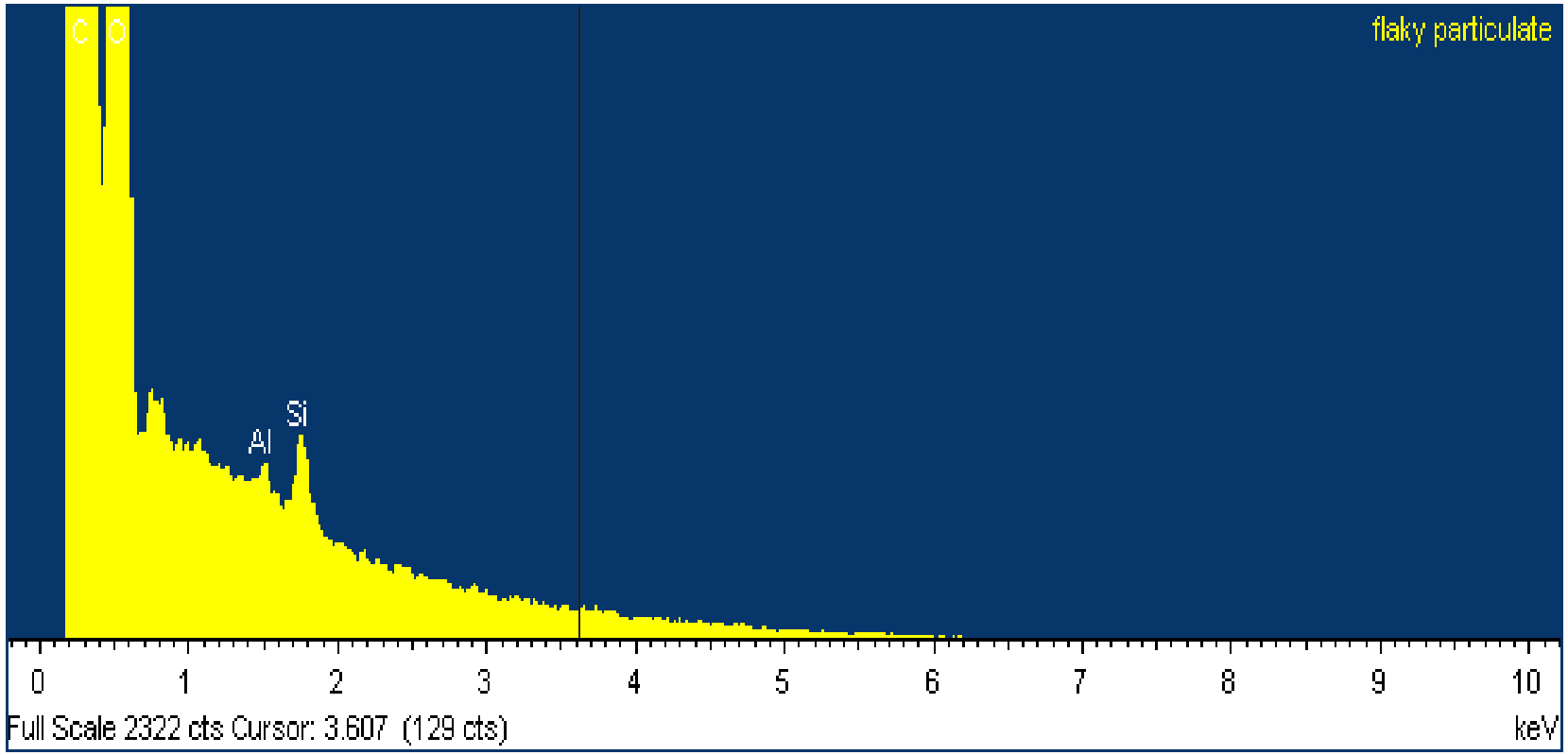
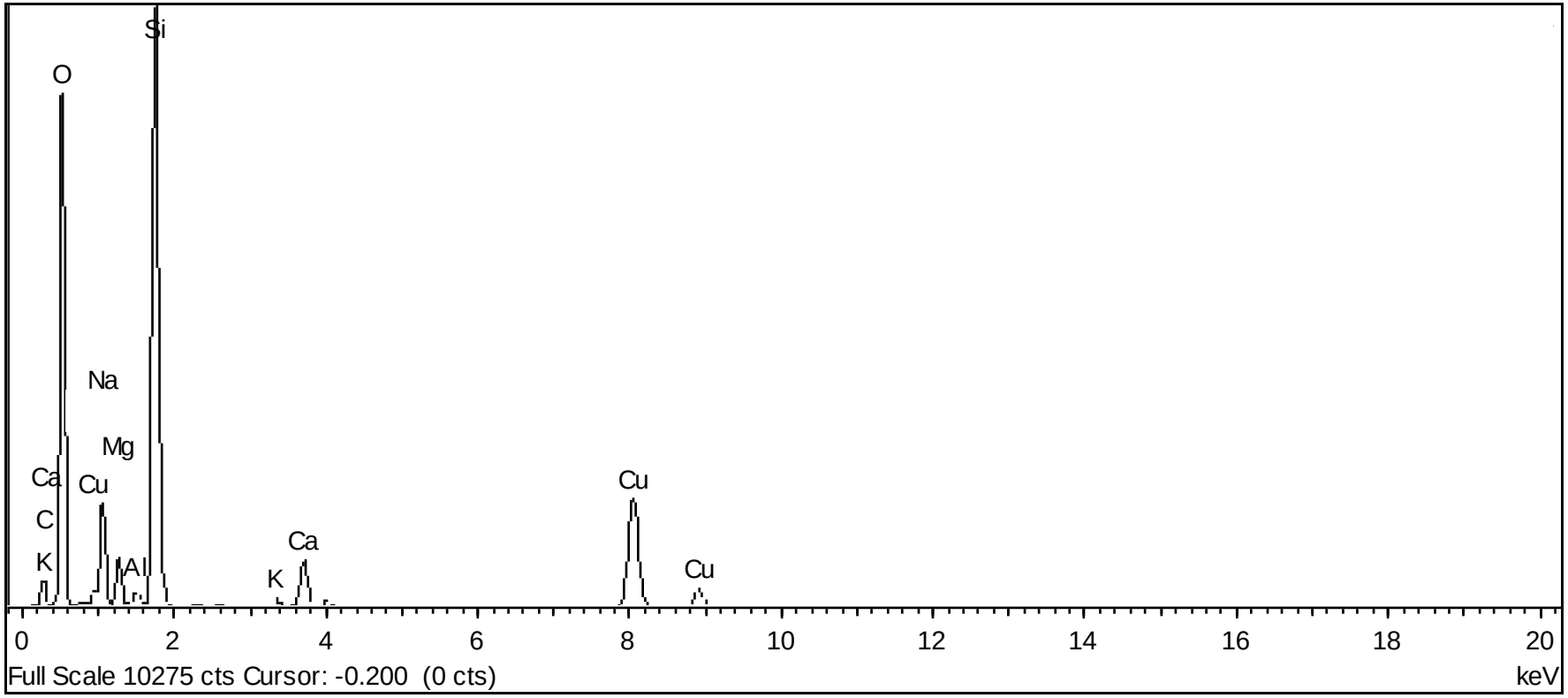
SEM/EDS of Flakes on Filter

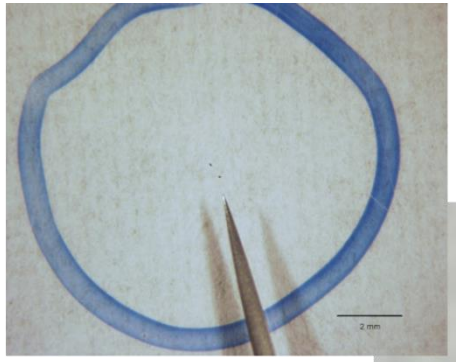


- Carbon signal from PC filter dominates spectrum
- Low accelerating voltage limits detection of higher energy X-rays

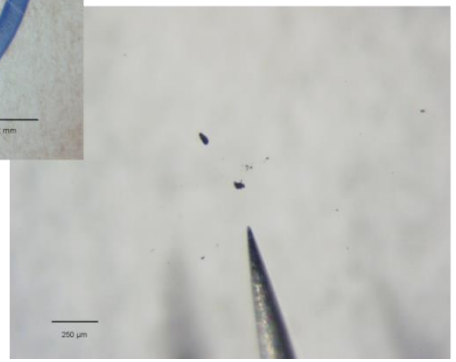
TEM/EDS of Flake on Grid



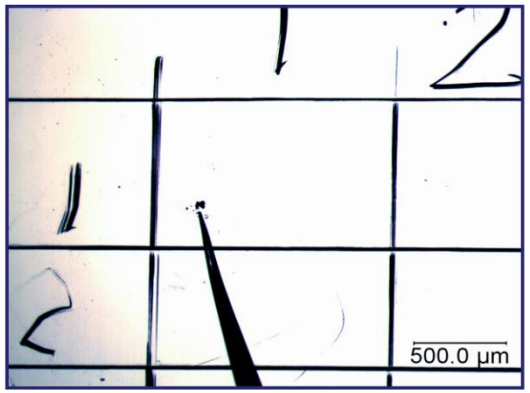
Direct Transfer of Particulate



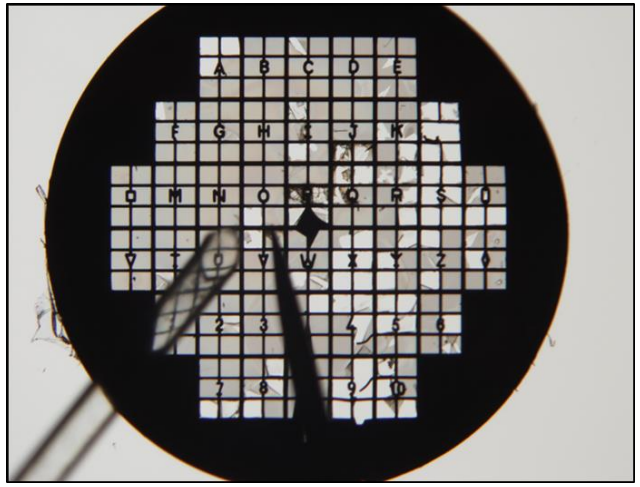
Area containing particulate circled on glass slide



Particulate viewed at higher magnification

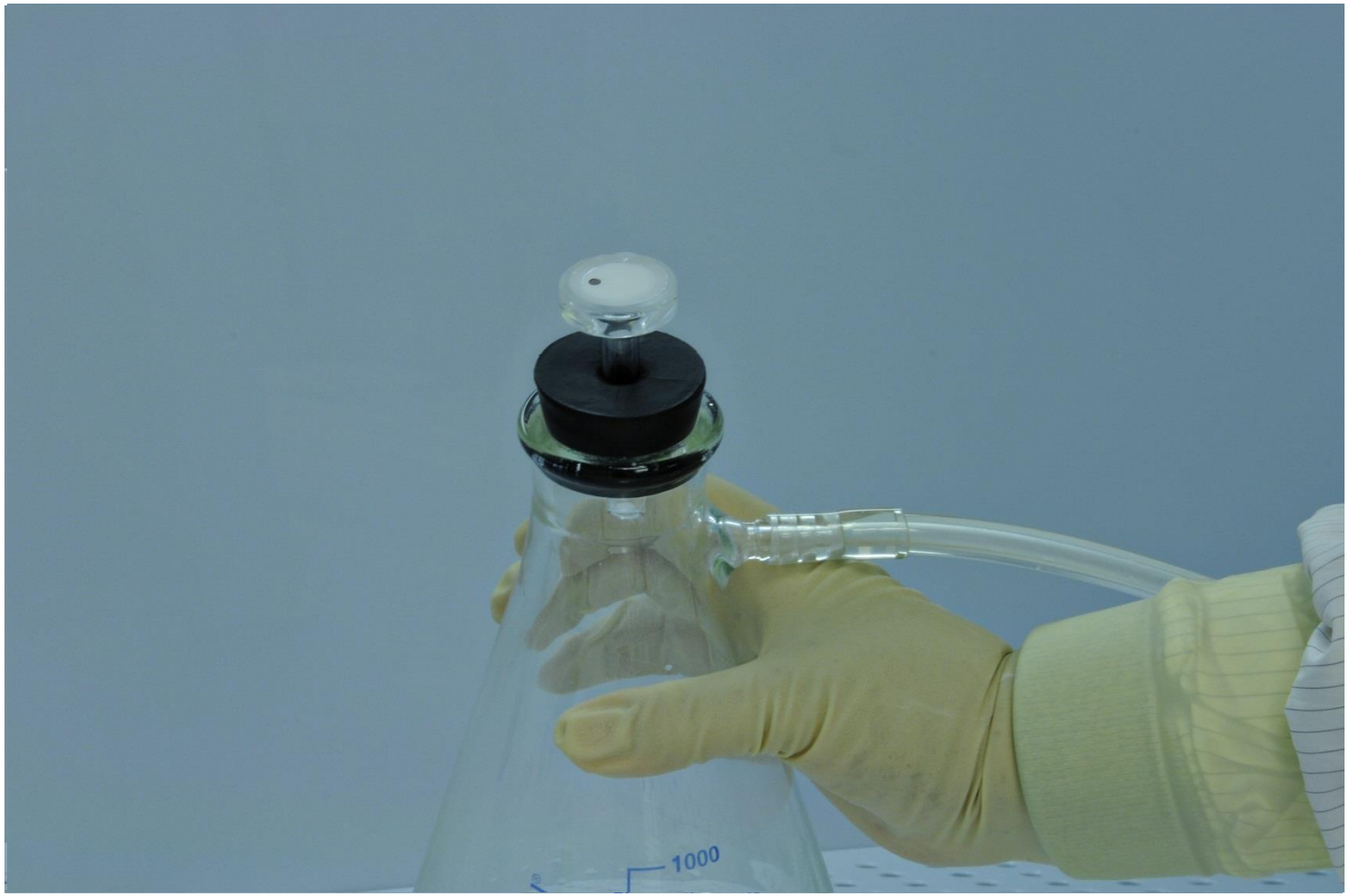


Transfer to SEM substrate



Transfer to TEM locator grid

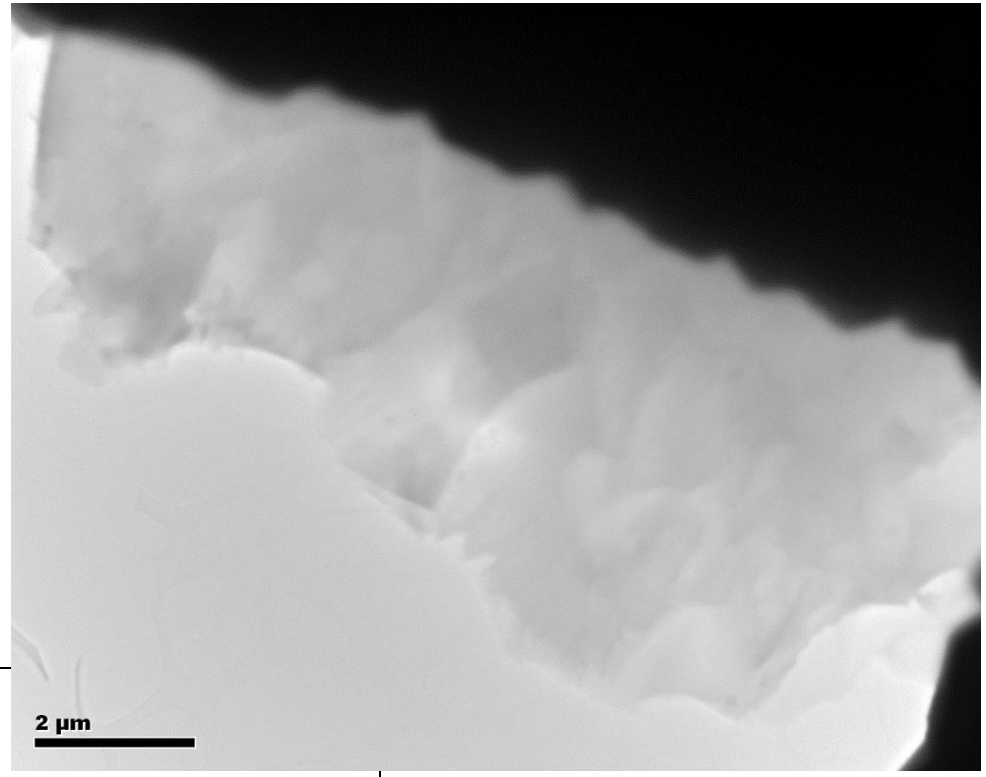
Filtration Onto a Holey Carbon Grid

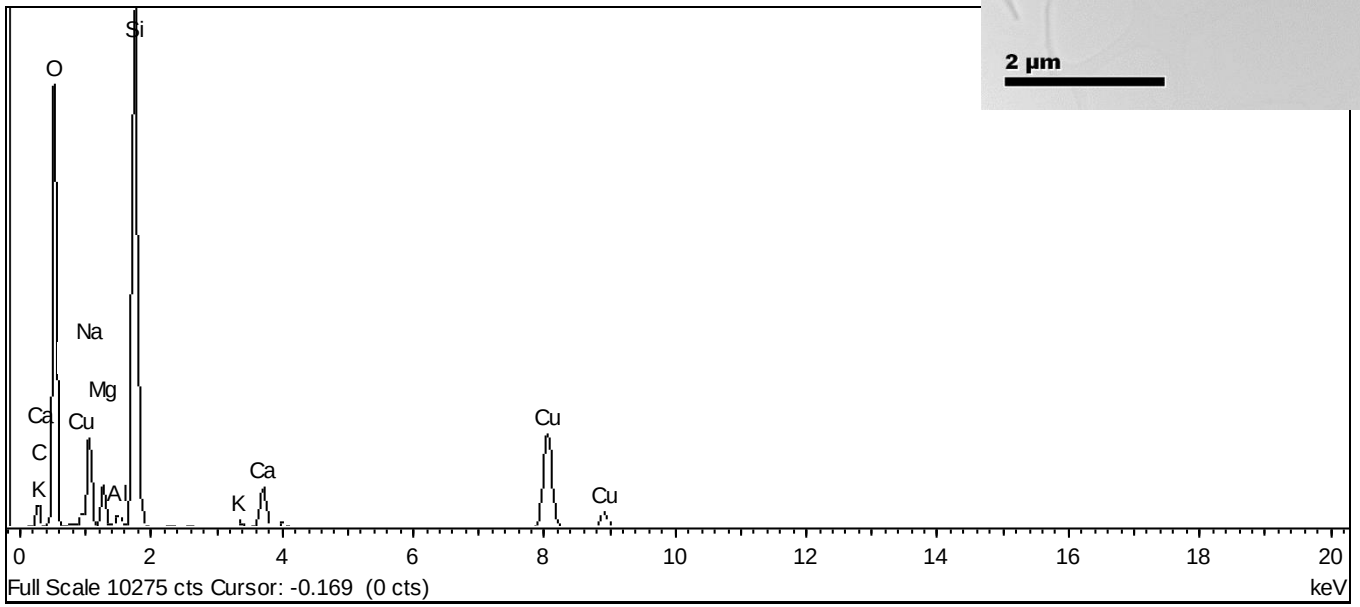


Comparison of SEM and TEM Findings for Filtered Samples

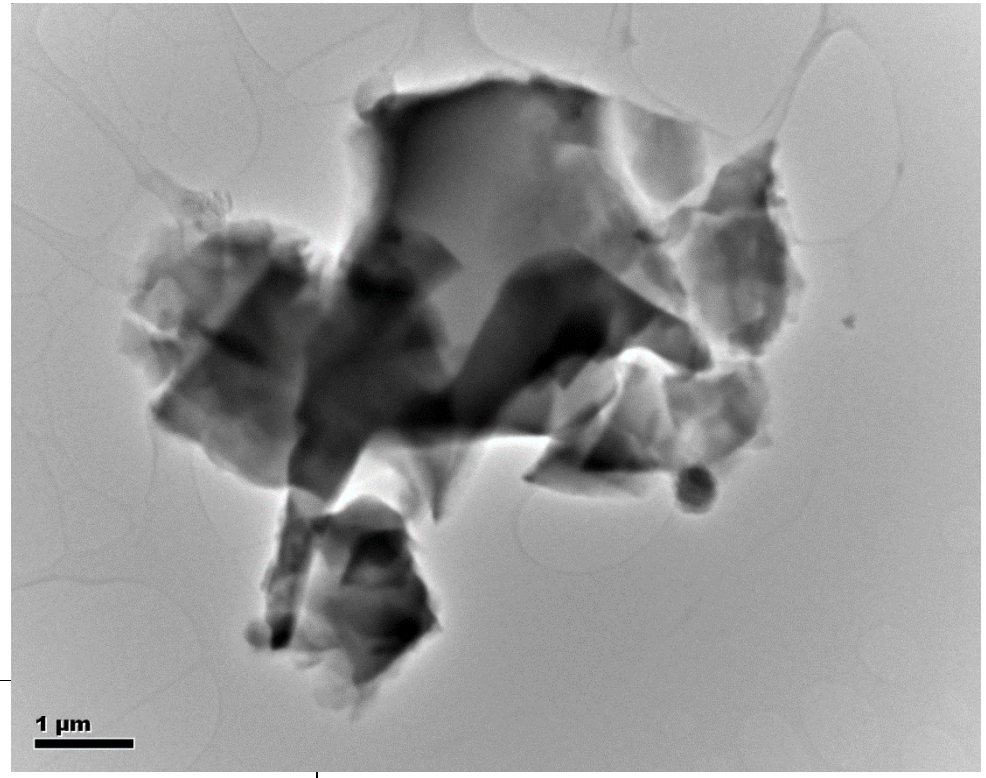
Sample	Vial 1 SEM	Vial 1 TEM
A	No flakes observed	Two delamination flakes
B	No flakes observed	Two delamination flakes
C	13 glass flakes observed	One large delamination flake
D	No flakes observed	A few C-rich particles, two possibly graphite

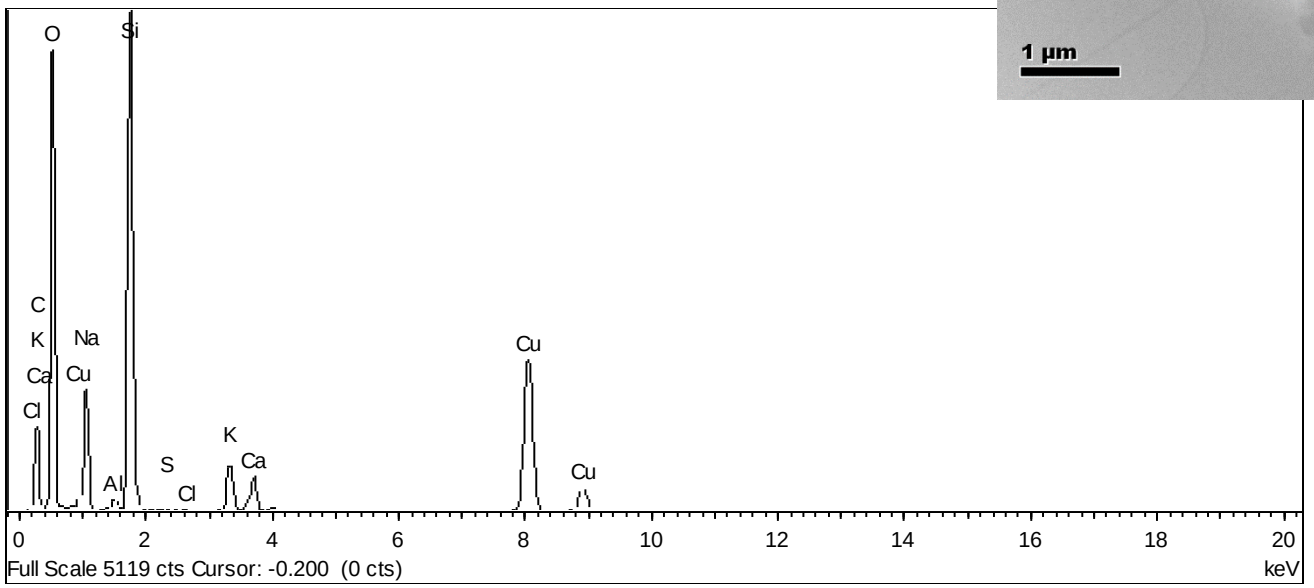
Delamination Flake Sample A



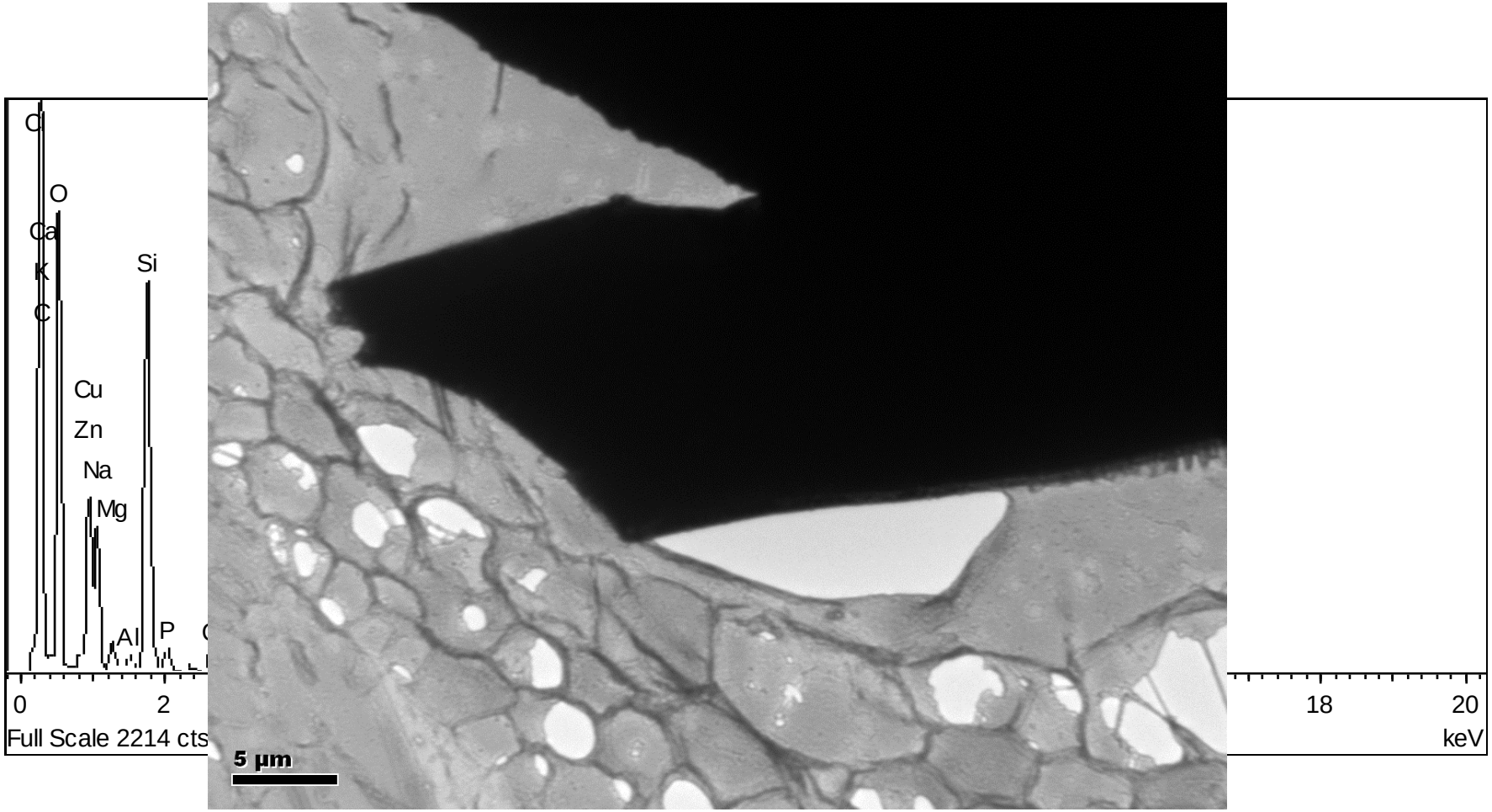


Delamination Flake Sample B

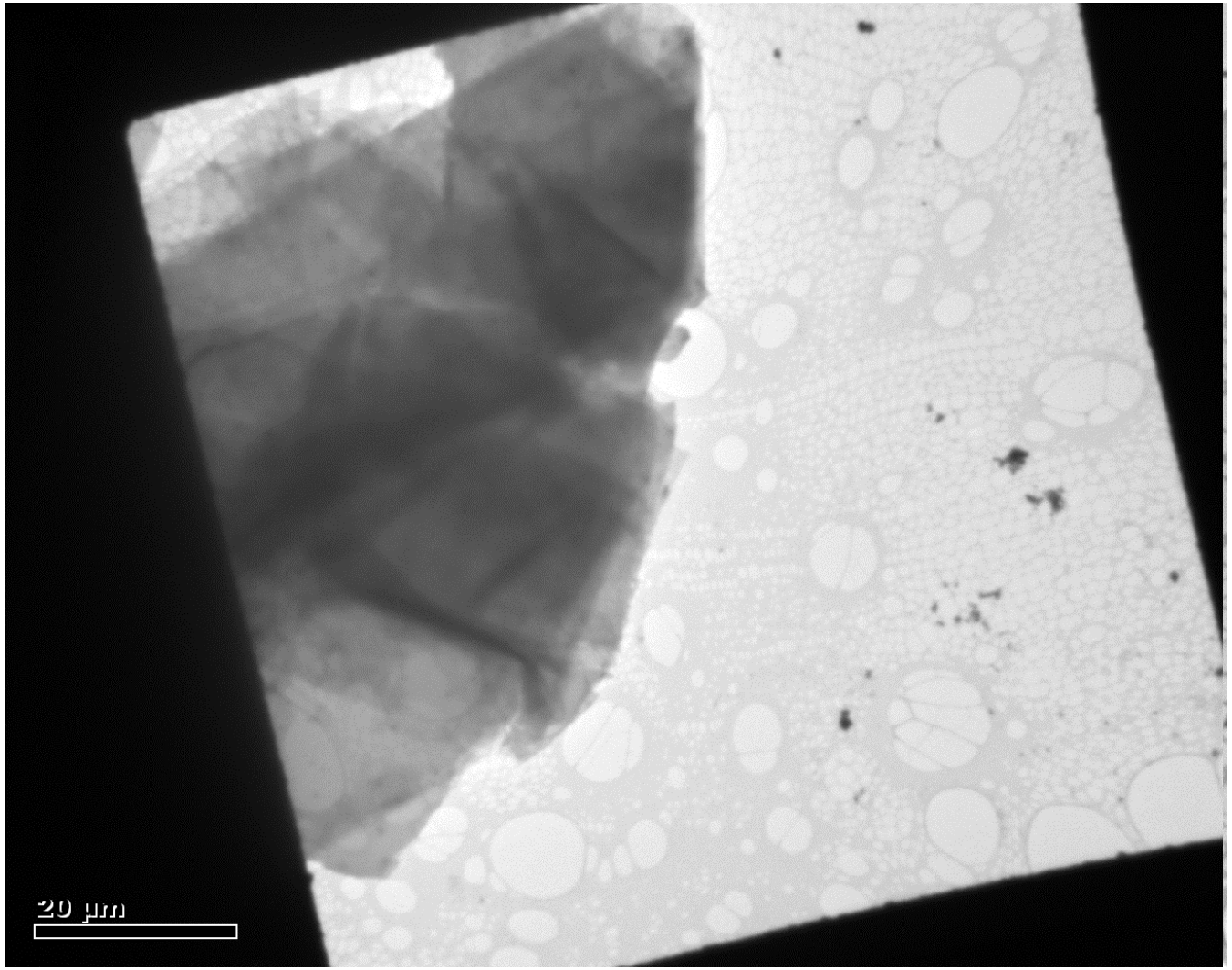




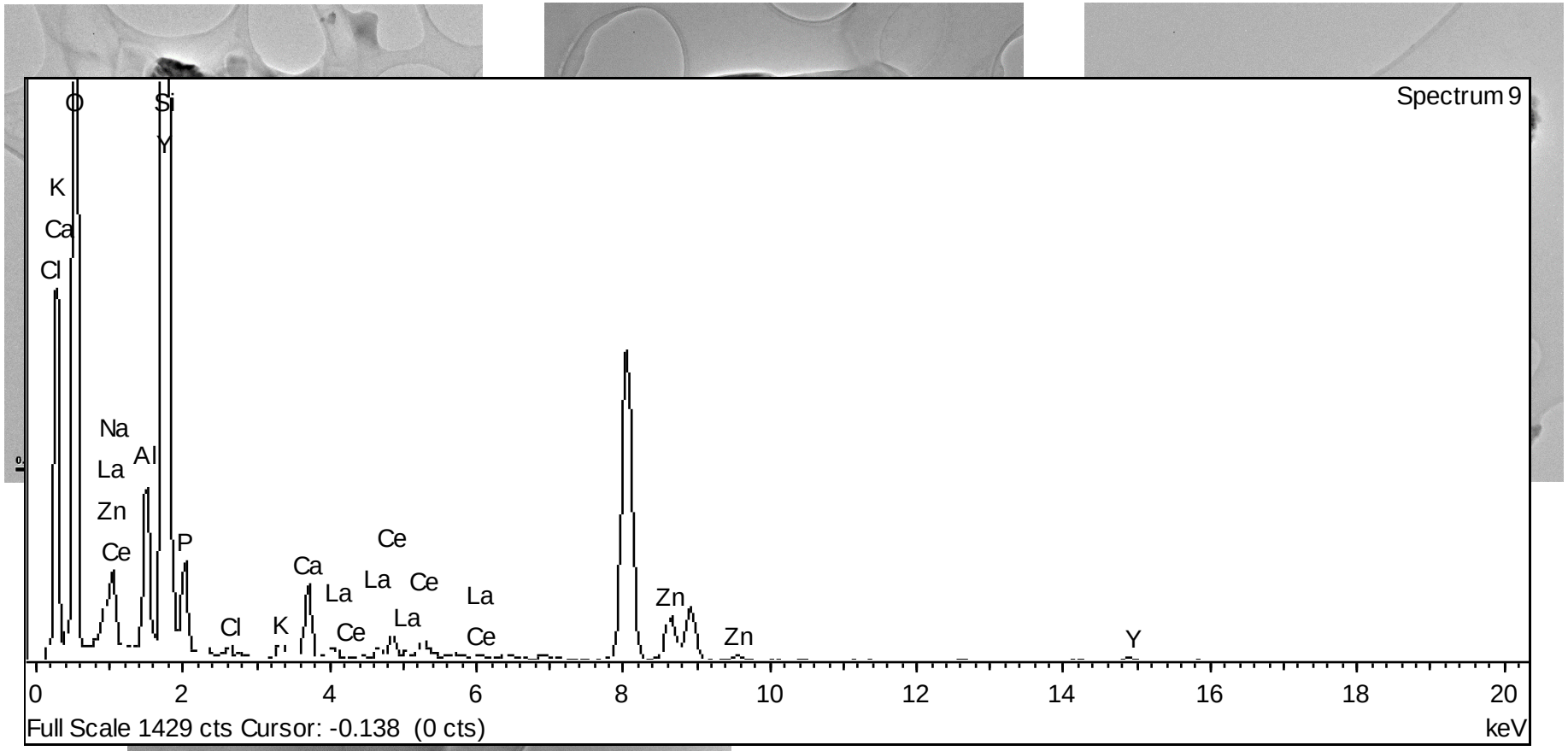
Delamination Flake – Sample C

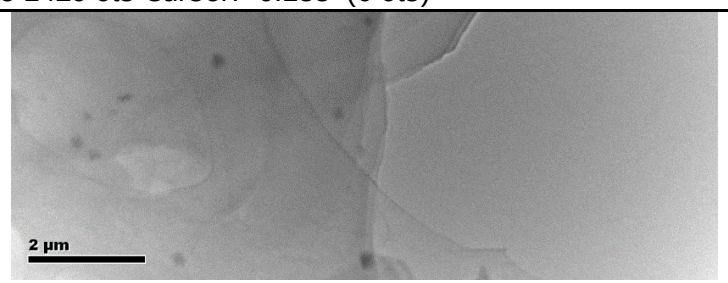


Filtered Particles



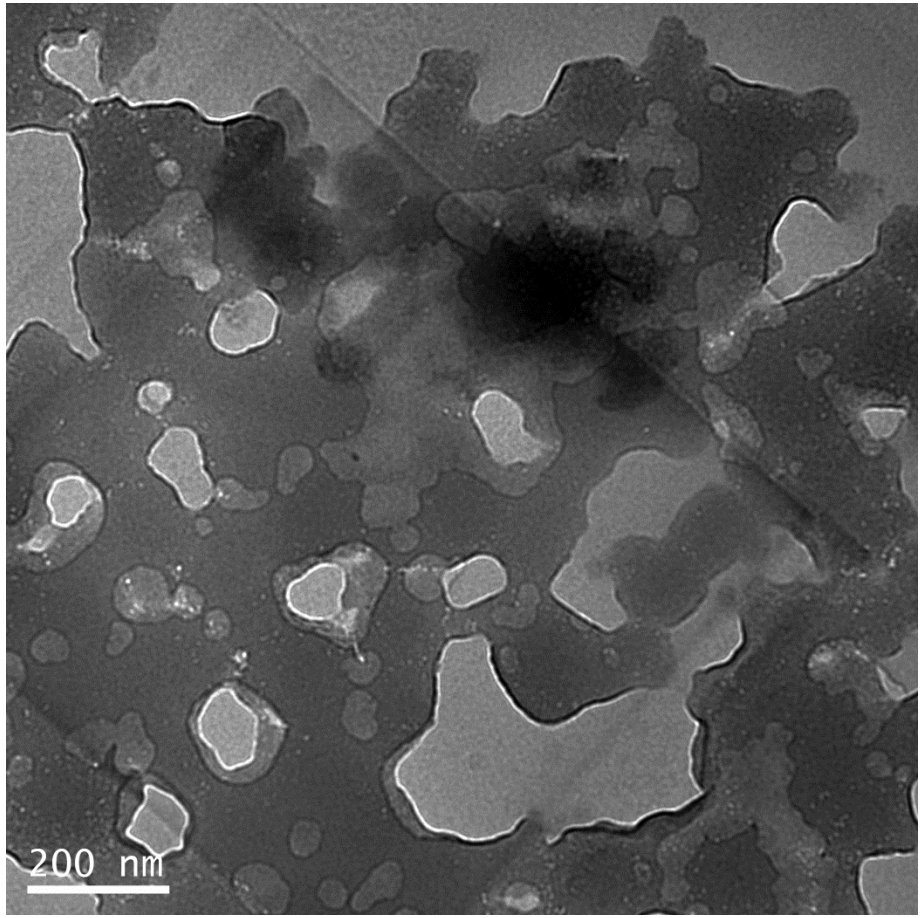
Filtered Particles

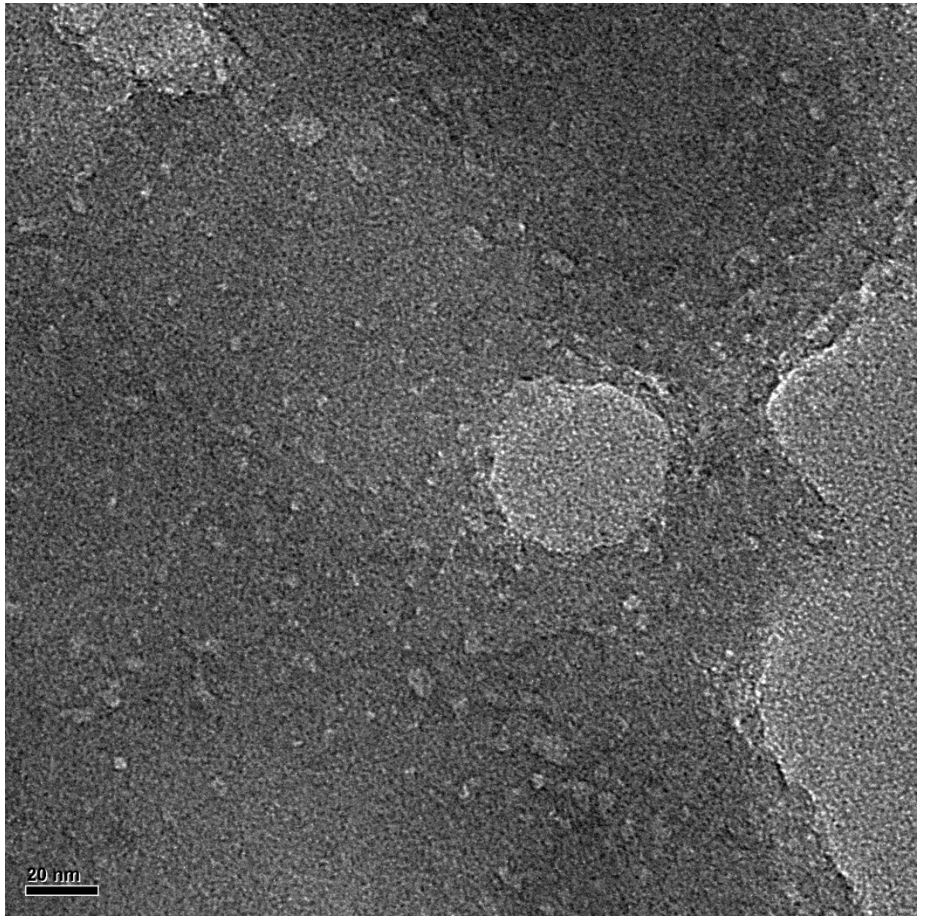




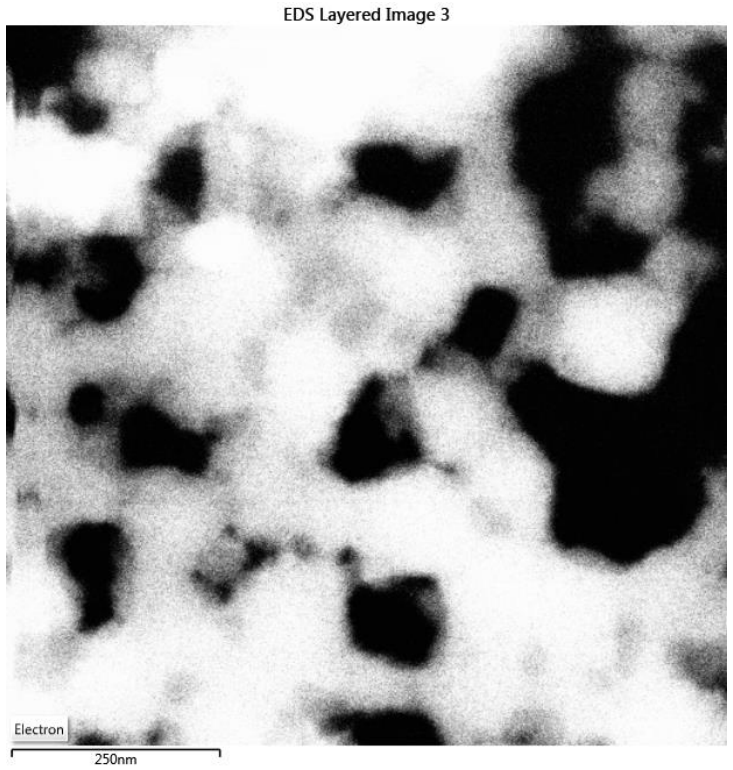
Left: Edge of glass delamination flake; dark spots are rich in phosphorus and REEs.

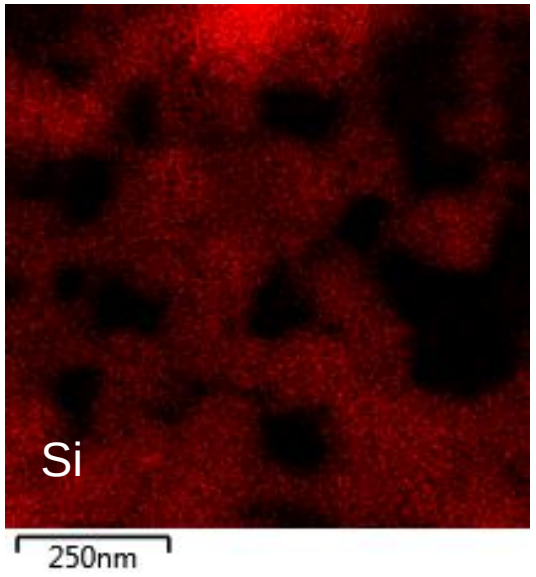
TEM Imaging of Porous Delamination Flakes

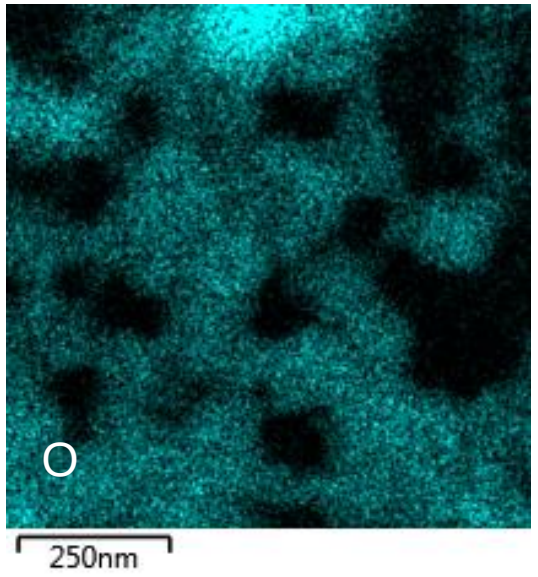


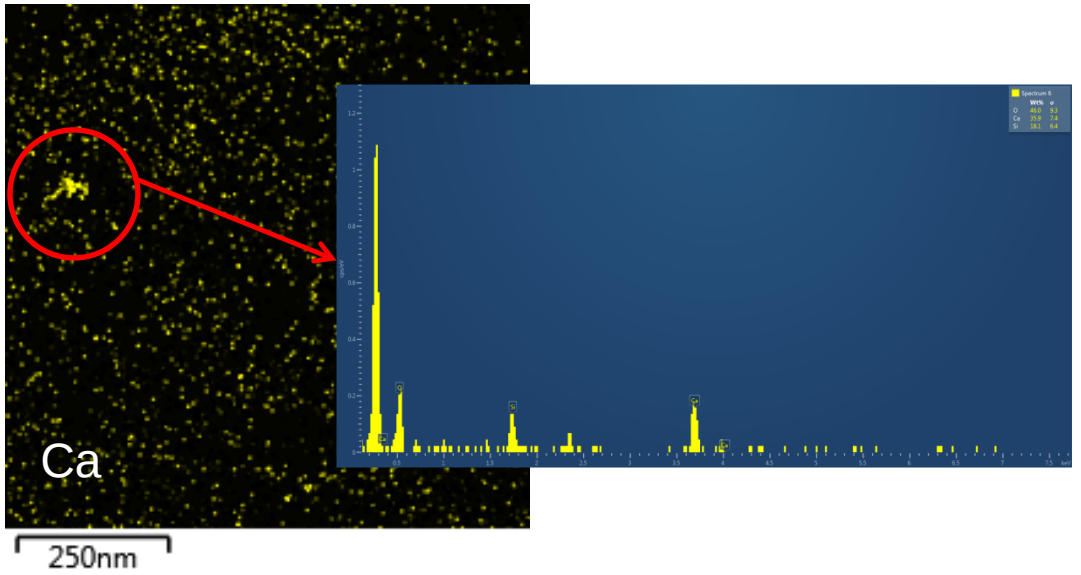


STEM EDS Mapping of Porous Delamination Flakes

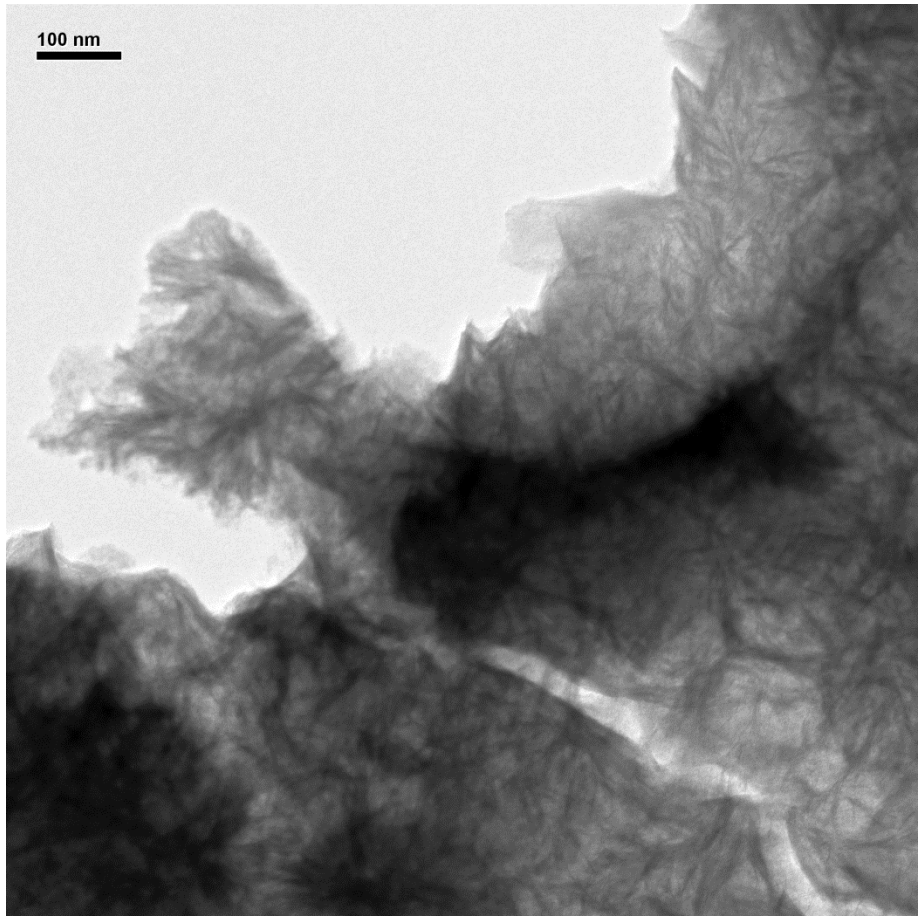


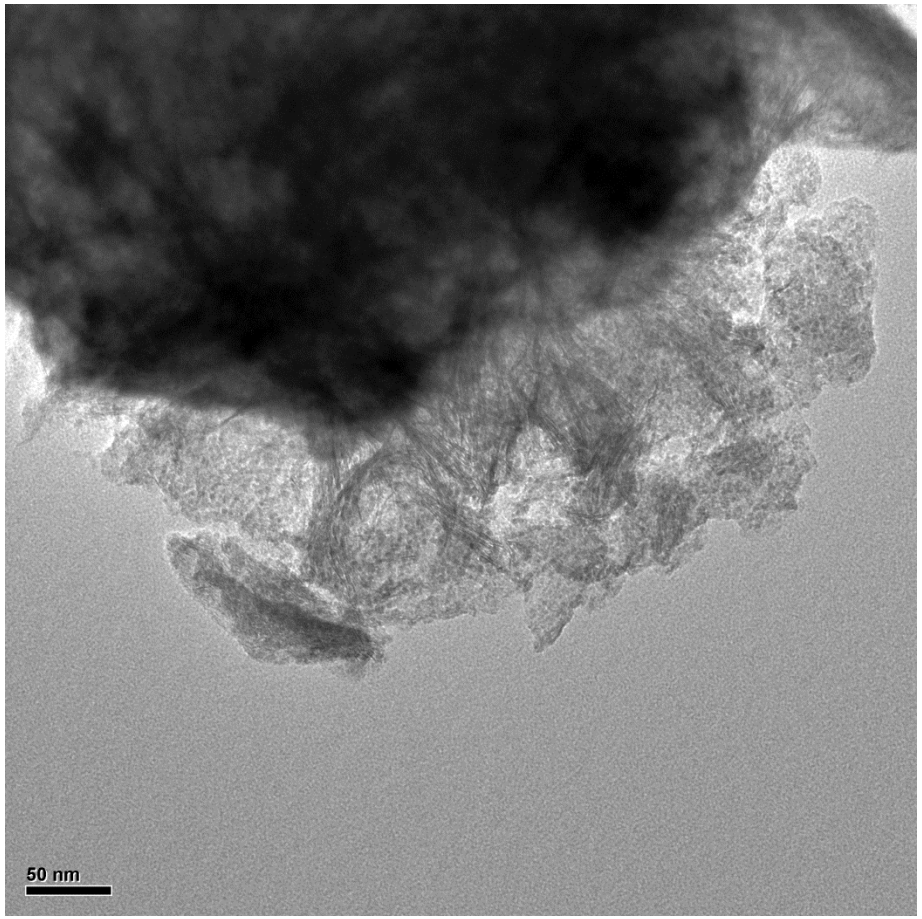






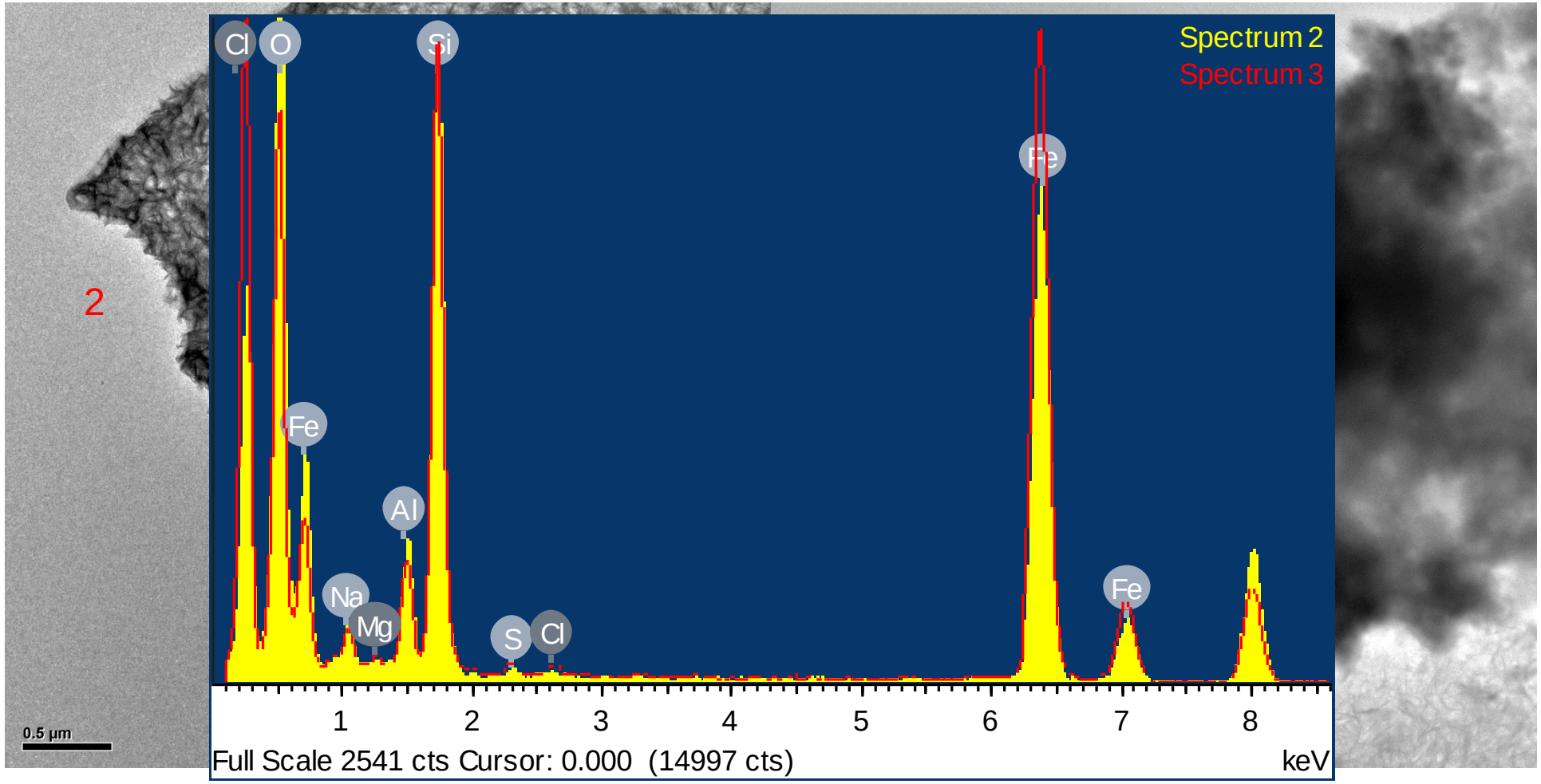
TEM Analysis of Secondary Products



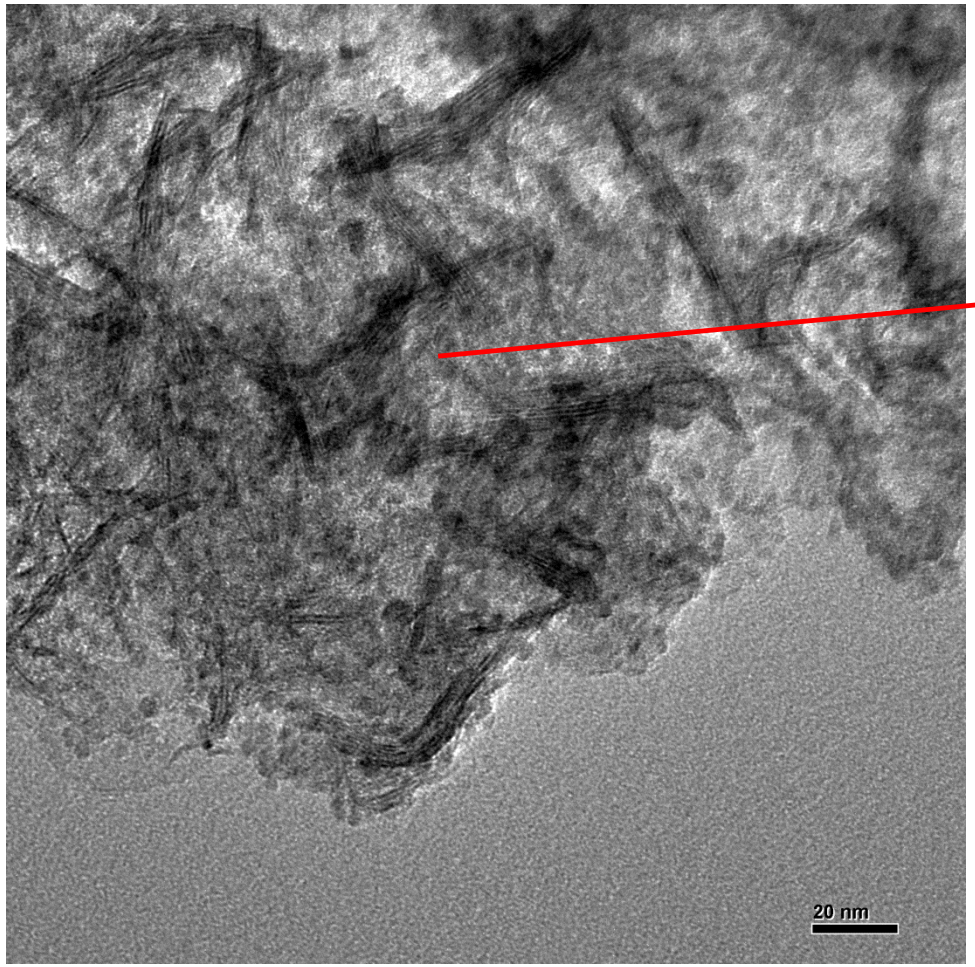


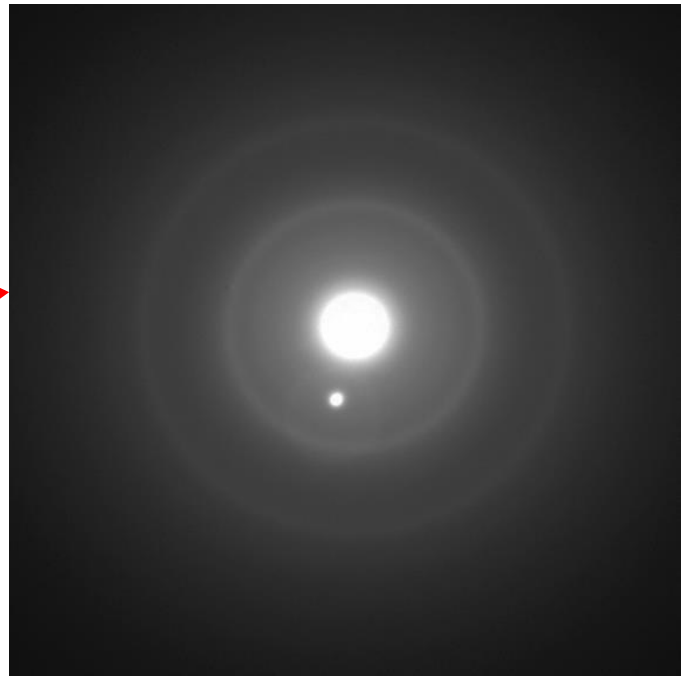
- Filtered from product containing delamination flakes
- Differentiated by light microscopy as brown particles

TEM Analysis of Secondary Products



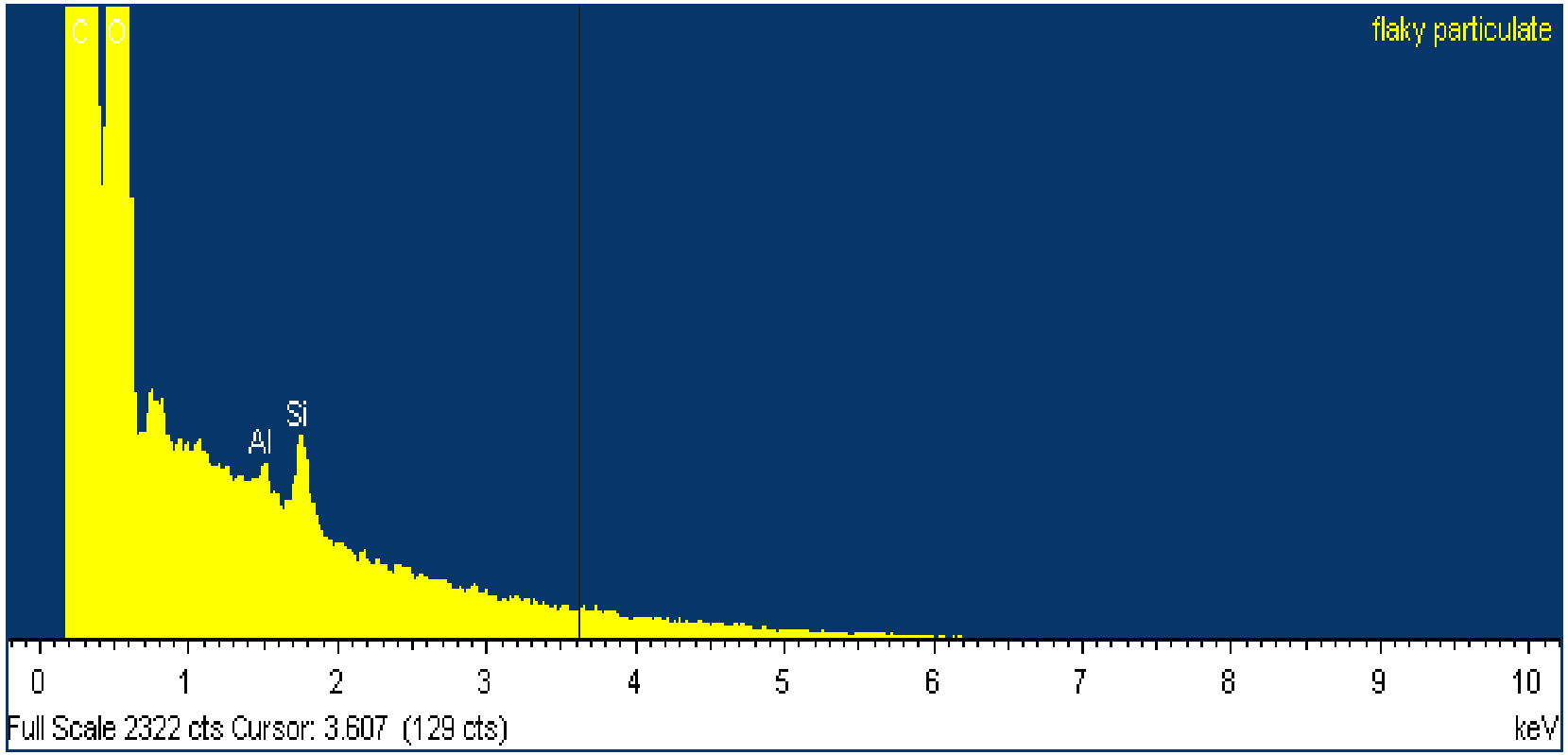
TEM Analysis of Secondary Products





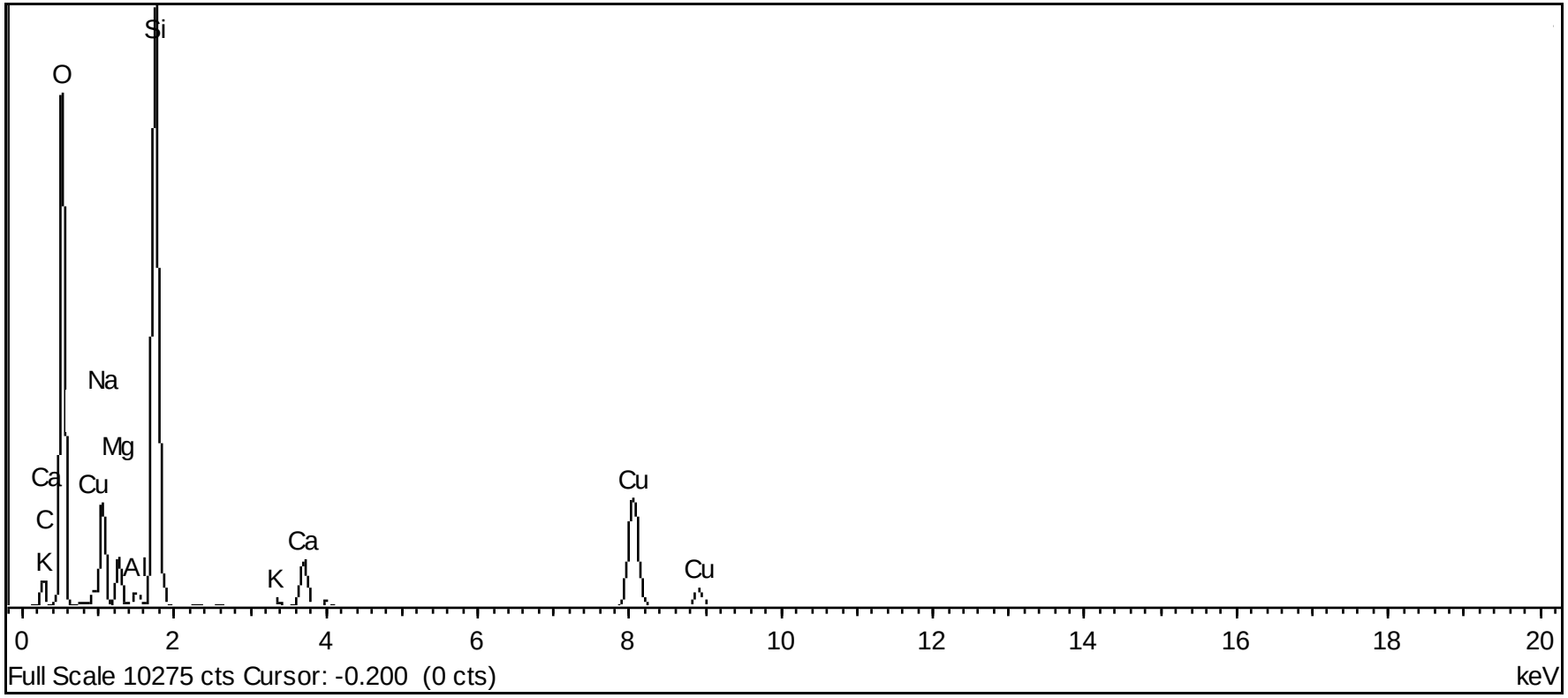
- Silicate with a distinct and uniform composition resulting from interaction of product with vial glass
- Ordered layer structure

SEM/EDS of Flakes on Filter



- Carbon signal from PC filter dominates spectrum
- Low accelerating voltage limits detection of higher energy X-rays

TEM/EDS of Flake on Grid



Conclusions

- Glass delamination is a complex process; understanding mechanisms is crucial to ensuring pharmaceutical product quality.
- TEM is an ideal technique for analysis of thin residues and particulate isolated from liquid pharmaceutical formulations, providing high resolution morphological, elemental and crystallographic information.
- Unambiguous TEM/EDS spectra can be obtained from flakes and residues that are too thin for SEM/EDS analysis.

Conclusions

- TEM grids can be prepared by direct transfer of glass delamination materials or by filtration. Filtration of vial contents onto holey carbon-coated TEM grids provides representative samples of particles, residues and delamination flakes.

- Detection of smaller and thinner flakes by TEM may aid in earlier detection of glass delamination.

- TEM complements routinely used techniques, and should be used in conjunction with them.

Questions?

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