Microsc. Microanal. 21 (Suppl 3), 2015
doi:10.1017/S1431927615002779 Paper No. 0198

Characterization of Glass Delamination by TEM: Results from a New Sample Preparation Technique

E.F. Schumacher[1], H.M. Talesky[1] and K.J. Diebold[1]

[1]McCrone Associates, Inc., Westmont, Illinois 60559 USA

Transmission electron microscopy with energy dispersive X-ray spectrometry (TEM/EDS) has been shown to offer advantages over scanning electron microscopy (SEM) with EDS for analysis of very thin particulate resulting from delamination of glass vials and syringes used in the pharmaceutical industry [1]. Delamination occurs when injectable solutions and suspensions react with glass packaging, resulting in contamination of drug products with glass flakes, coatings, and residues formed from glass dissolution or reaction with the drug to form a secondary product. Particulate is typically isolated from liquid products by filtration, followed by examination using light microscopy. The filtered particulate may then be analyzed using SEM/EDS, a technique recommended for use in glass container screening studies as outlined in USP <1660> [2, 3].

Examination of glass surfaces and isolated particulate using light microscopy and SEM may be sufficient to confirm that glass delamination has occurred. However, elemental analysis can be critical in determining whether particulate in a liquid product is glass delamination, glass coating, dissolved glass residue or a secondary product. Removal of extremely thin samples from filters for transfer to SEM substrates can be difficult. An alternative is to mount the entire filter on a substrate. Either preparation technique typically results in EDS spectra dominated by a signal from the substrate or the carbon filter, and containing much smaller peaks for major particulate components. Peaks for minor or trace elements may be entirely absent, thereby lessening the value of EDS for discrimination between glass and other materials that may be present.

Though the TEM is ideal for characterization of these very thin samples, transfer of flakes and residues from filters to TEM grids can be challenging. A method has been developed whereby filtration of liquid products directly onto holey carbon-coated TEM grids captures a sufficient amount of representative material to identify particulate isolated from liquid products. Results were found to be largely consistent with those obtained by SEM/EDS analysis of concurrently filtered products mounted on SEM substrates. More complete information about particulate elemental composition was obtained by TEM analysis, and in two cases, glass delamination flakes were captured on TEM grids but were not found on SEM substrates prepared from the same filtrations.

Little to no background particulate was found when as-received grids and blanks grids prepared by filtration of particle-free water were examined. Characteristics of particulate isolated from an iron sucrose product were consistent with results of earlier TEM studies in which grids were prepared by direct transfer of the material rather than by filtration [1]. Delamination flakes and other types of contaminant particles filtered directly onto grids were unambiguously identified using TEM/EDS.

TEM/EDS characterization of materials associated with glass delamination can verify composition in samples too thin for SEM/EDS analysis. Detection of smaller and thinner flakes may also aid in earlier detection of glass delamination. Though SEM is of value for analysis of bulk glass and some

types of associated particulate, this work demonstrates the benefit of TEM for unambiguous characterization of thin particulate and residues associated with glass delamination processes.

References:

[1] Schumacher, et al., Proc. Microscopy and Microanalysis 2012.
[2] Haines, D., et al., *Contract Pharma*, published online June 2013.
[3] General Chapter <1660> Evaluation of the Inner Surface Durability of Glass Containers, available online from the U.S. Pharmacopeial Convention.

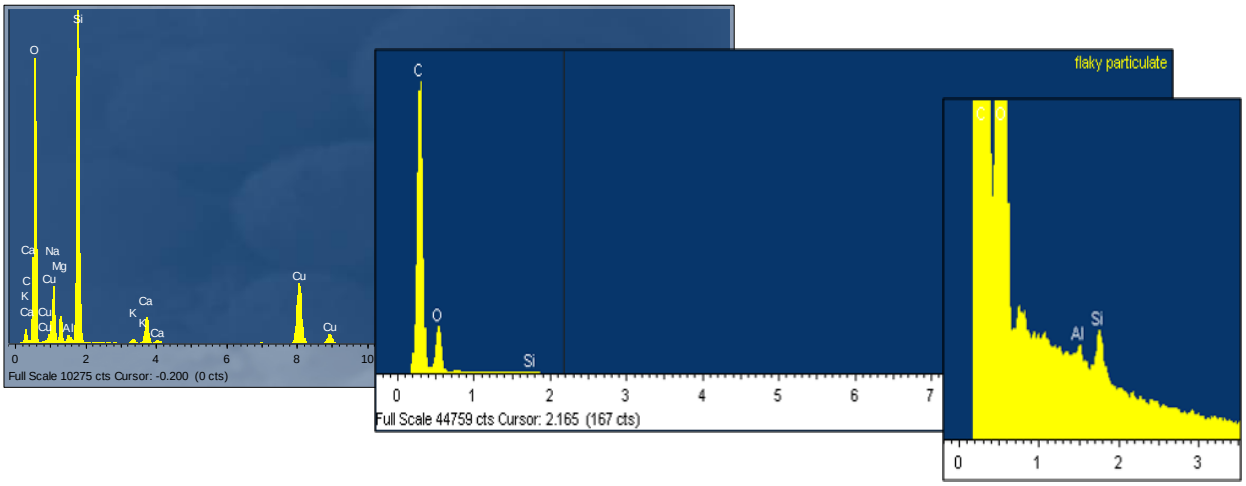

Fig. 1. TEM EDS spectrum from glass delamination flake (left), and SEM EDS spectrum from similar flake (center). SEM spectrum Y-axis expanded to show peaks from glass elements (right).

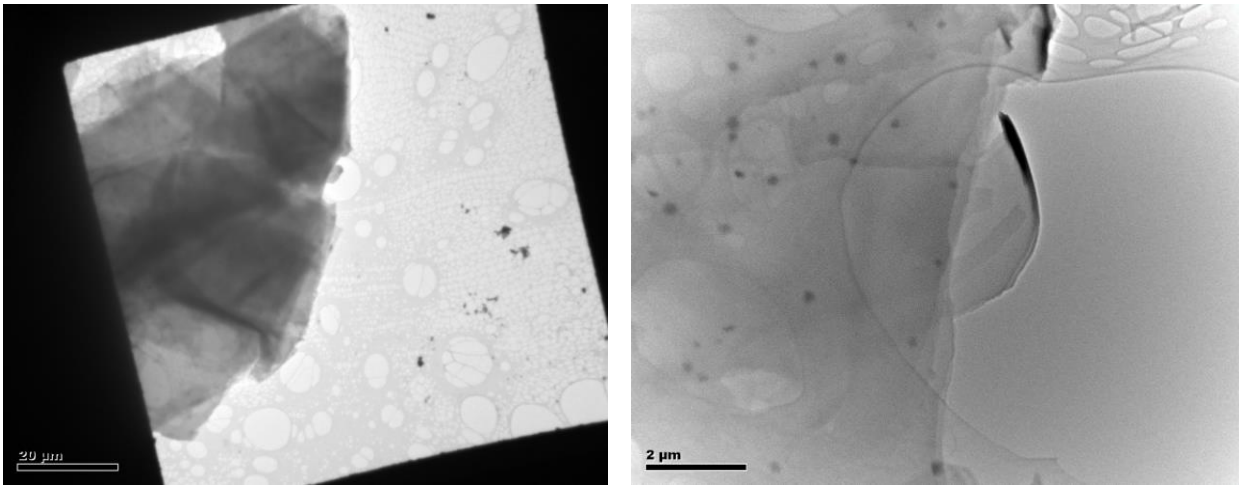

Fig. 2. TEM images of delamination flakes captured on holey carbon grids by filtration. Dark spots in image on right were found to be rich in phosphorus and rare earth elements.