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Identification of Pharmaceutical Constituents in Finished Product Form Using Low kV Microanalysis

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Microanalysis of pharmaceutical tablets in finished form has been successfully demonstrated to provide beneficial analytical results which reveal local chemistry distributions and constituent elemental analysis. The phase mapping approach of Scanning Electron Microscopy and Energy Dispersive Spectroscopy (SEM EDS) collection shows compounds of associated elements, their size, distribution and morphological characteristics throughout a tablet's form [1]. Impurities and degradants can be located, identified and studied in their local chemical environment, leading to further understanding of their mechanisms of formation [2]. Earlier work provides sufficient information to make determinations on presence of compounds of interest, however, matrix components are routinely observed in the data due to the size of the analytical volume of the electron beam and resultant x-ray signal. Therefore, collection optimization to reduce the microvolume to the compounds of interest will provide a more distinct analysis of the intended components. Low kV SEM EDS microanalysis provides the conditions necessary for the collection of data from smaller, spatially-specific sites.

Electron beam energies at or below 8 kV have sufficient energy to overcome the electron binding energy needed to create an X-ray event in many materials, yet lose energy as the beam penetrates into the sample. The loss of primary beam energy with increased depth and width reduces the ionization potential and therefore reduces the number of X-rays generated outside of the primary beam area. With that understanding, analytical conditions are chosen to match the lower spatial needs for this work, while still providing the excitation capability. The benefits include reduction of matrix contribution which confines the signal to the desired compound and reduced absorption from the sample matrix which then increases detectability. Increased detection increases efficiency, distinguishes specific areas and provides a better basis for component isolation. Multi-spectrum collection from fine particulates shows two different compounds, Ferrous Sulfate and DiCalcium Phosphate in a cross section of Iron supplement tablet, Fig 1.

Electron beam energies at or below 5 kV can be used for spectral analysis of very fine particulates of active ingredient or impurities. At these lower energies, the x-ray excitation is more difficult to achieve for certain core shell electrons, such as the Sulfur and Iron in the tablet mentioned previously. S L and Fe L x-rays must be utilized which is possible with high performance resolution advances in Silicon Drift Detector technology. Spectral data obtained with EDAX Octane SDDs verifies the presence of smaller Ferrous Sulfate areas by detecting the lower energy S L and Fe L X-ray peaks, Fig 2.

Wavelength Dispersive Spectroscopy, WDS, can then be employed to further confirm the low energy elemental results. WDS adds an additional benefit to EDS analysis, in particular at low kV, for peak resolutions below 15 eV. At low kV, elemental lines such as Fe L and O K, or S L

at 0.149 keV and P L at 0.100 keV lines are desirable to be used and WDS has sufficient resolution to properly separate them, Fig 3. WDS is further shown to have benefit for increased sensitivity for low energy elements such as nitrogen, a common constituent that can be difficult to optimize collection for and detect with EDS.

Low kV microanalysis provides smaller spatial analytical volumes within a pharmaceutical product's finished form and reduced signal from beam spread and matrix constituents. In order to achieve analysis at the needed low beam kV, lower x-ray energy lines must be analyzed, which is possible with current high performance EDS SDDs. WDS analysis provides a further benefit of more conclusive low energy peak separation and increased sensitivity for elements difficult with EDS.

References:

[1] Anderhalt *et al*, Microscopy & Microanalysis Proceedings (2010).
[2] Nylese *et al*, Microscopy & Microanalysis Proceedings (2011).

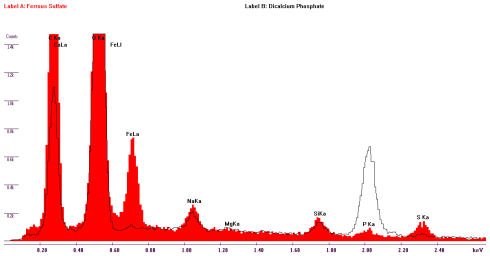

Figure 1. EDS Spectrum overlay at 5 kV two components, with distinct FeL and S K in red and P K in outline. The ferrous sulfate particle was measured to be 1.5 um in diameter.

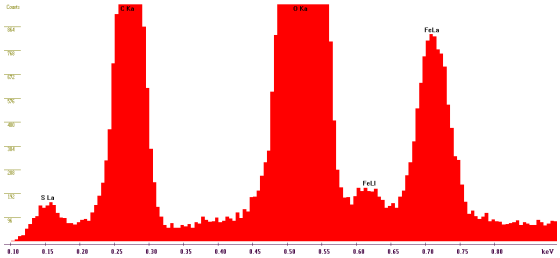

Figure 2. Spectrum of Ferrous Sulfate Area at 5 kV showing low energy S L and FeL peaks.

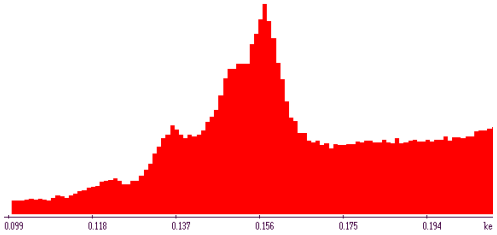

Figure 3. WDS spectrum, right, shows low energy in greater detail.

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