MILLIMETER-WAVE SPECTROSCOPY FOR ANALYTICAL CHEMISTRY: THERMAL EVOLUTION OF LOW VOLATILITY IMPURITIES AND DETECTION WITH A FOURIER TRANSFORM MOLECULAR ROTATIONAL RESONANCE SPECTROMETER (TEV FT-MRR)

BRENT HARRIS, SHELBY S. FIELDS, JUSTIN L. NEILL, ROBIN PULLIAM, MATT MUCKLE, *BrightSpec Labs, BrightSpec, Inc., Charlottesville, VA, USA*; BROOKS PATE, *Department of Chemistry, The University of Virginia, Charlottesville, VA, USA*.

Recent advances in Fourier transform millimeter-wave spectroscopy techniques have renewed the application reach of molecular rotational spectroscopy for analytical chemistry. We present a sampling method for sub ppm analysis of low volatility impurities by thermal evolution from solid powders using a millimeter-wave Fourier transform molecular rotational resonance (FT-MRR) spectrometer for detection. This application of FT-MRR is relevant to the manufacturing of safe oral pharmaceuticals. Low volatility impurities can be challenging to detect at 1 ppm levels with chromatographic techniques. One such example of a potentially mutagenic impurity is acetamide (v.p. 1 Torr at 40 C, m.p. 80 C). We measured the pure reference spectrum of acetamide by flowing the sublimated vapor pressure of acetamide crystals through the FT-MRR spectrometer. The spectrometer lower detection level (LDL) for a broadband (¿ 20 GHz, 10 min.) spectrum is 300 nTorr, 30 pmol, or 2 ng. For a 50 mg powder, perfect sample transfer efficiency can yield a w/w % detection limit of 35 ppb. We extended the sampling method for the acetamide reference measurement to an acetaminophen sample spiked with 5000 ppm acetamide in order to test the sample transfer efficiency when liberated from an pharmaceutical powder. A spectral reference matching algorithm detected the presence of several impurities including acetaldehyde, acetic acid, and acetonitrile that evolved at the melting point of acetaminophen, demonstrating the capability of FT-MRR for identification without a routine chemical standard. The method detection limit (MDL) without further development is less than 10 ppm w/w %. Resolved FT-MRR mixture spectra will be presented with a description of sampling methods.