**Poster Presentation**

**MS72.P01**

## *PPM Detection Limits in PXRD by Integrating Nonlinear Optics and Synchrotron XRD*

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SHG microscopy allows rapid and selective identification of trace chiral crystals within amorphous media, enabling targeted XRD using a 5-10 micrometer diameter "minibeam". The sensitivity of PXRD is increased substantially by reducing the background scattering contributions of amorphous material otherwise encountered with a larger beam. In addition, performing diffraction only at the locations most likely to produce diffraction greatly reduced the overall beam-time required to perform the PXRD analyses. Integration of the SHG microscope directly into a synchrotron X-ray beamline at Argonne National Laboratory recovered high spatial registry between the regions of interest identified by SHG for positioning within the X-ray beam. Using this approach, diffraction was performed on individual griseofulvin nanocrystals suspended within an amorphous polymer, corresponding to a total of ~20 fg of total crystalline material. Additional measurements for ritonavir in hydroxypropylmethylcellulose (HPMC) were also performed, in which a bulk API concentration of 100 ppm produced diffraction peaks with a signal to noise ratio of >3000. Among other applications, sensitive detection of trace crystallinity can inform the design of amorphous formulations, in which the bioavailability of active pharmaceutical ingredients (APIs) is enhanced by maintaining them in an amorphous state. However, the long-term stability of a final dosage form can be negatively impacted by spontaneous transitioning to the typically more stable crystalline forms of the APIs, such that extensive quantitative characterization of the crystallization behaviors of amorphous formulations is routinely performed.

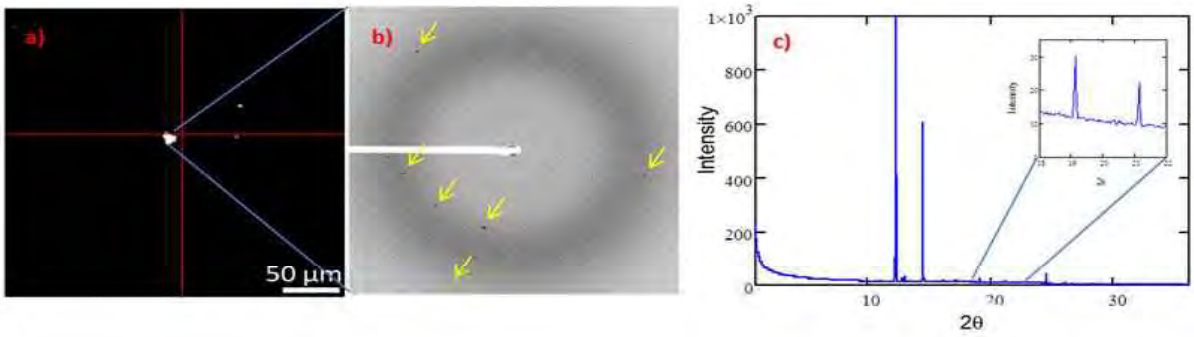


Figure 4. Strategy for trace crystal detection of 0.01% ritonavir in HPMC by combining SHG microscopy with synchrotron XRD: a) SHG micrograph acquired using the integrated instrument at the Advanced Photon Source in Argonne National Laboratory, b) scattering pattern collected from a single 5µm by 5 µm column through the sample including the region of interest identified by SHG, c) corresponding diffraction pattern after azimuthal autocorrelation of the image in b) to remove diffuse scattering contributions. The inset in c is a zoom-in showing clearly detectable diffraction for peaks only ~10 units in amplitude.

**Keywords:** powder X-ray diffraction, Detection limits, active pharmaceutical ingredient