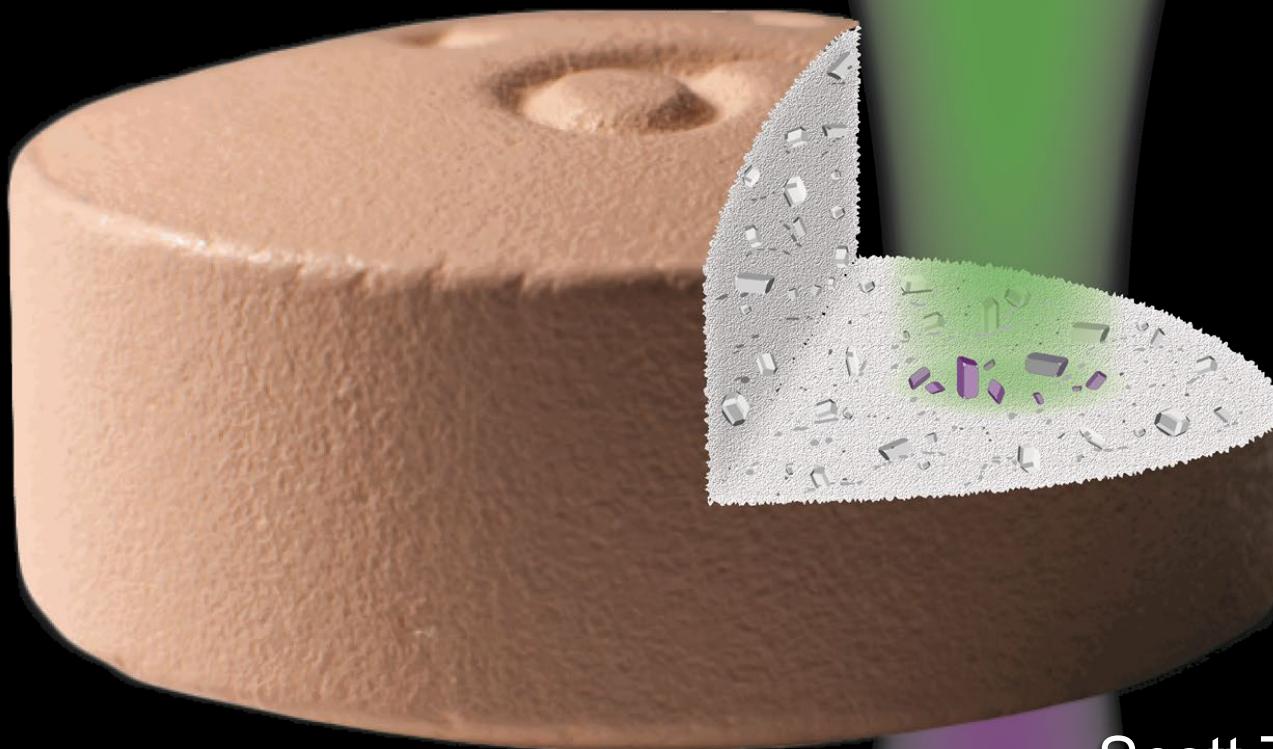




SELECTIVE IMAGING OF APIs IN POWDERED BLENDS WITH COMMON EXCIPIENTS UTILIZING TPE-UVF AND UV-SONICC



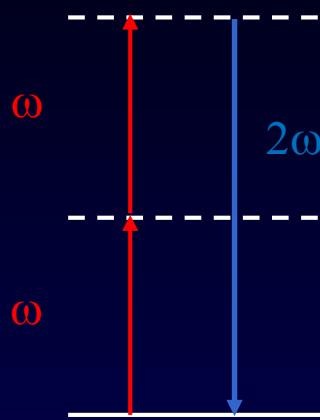
Scott Toth
Purdue University
Department of Chemistry



Comparison of Techniques for API Analysis

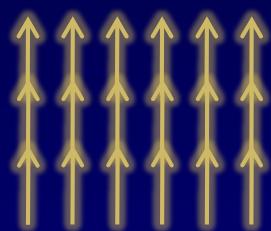
- Brightfield Microscopy
 - Fast, not selective
- Raman Microscopy
 - Selective but time-consuming
- X-ray Powder Diffraction
 - High LOD (~1%)
- SEM
 - Not real-time
- Calorimetry
 - High LOD

Second Harmonic Generation



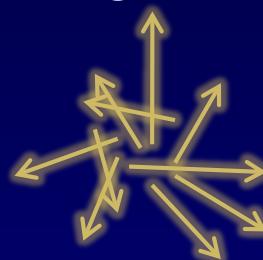
- Second Harmonic Generation (SHG) occurs only in the presence of well-ordered crystals
 - Chiral, noncentrosymmetric
- No SHG results from the interaction with amorphous materials

SHG active



Chiral crystals

SHG inactive



Liquid, glass,
amorphous

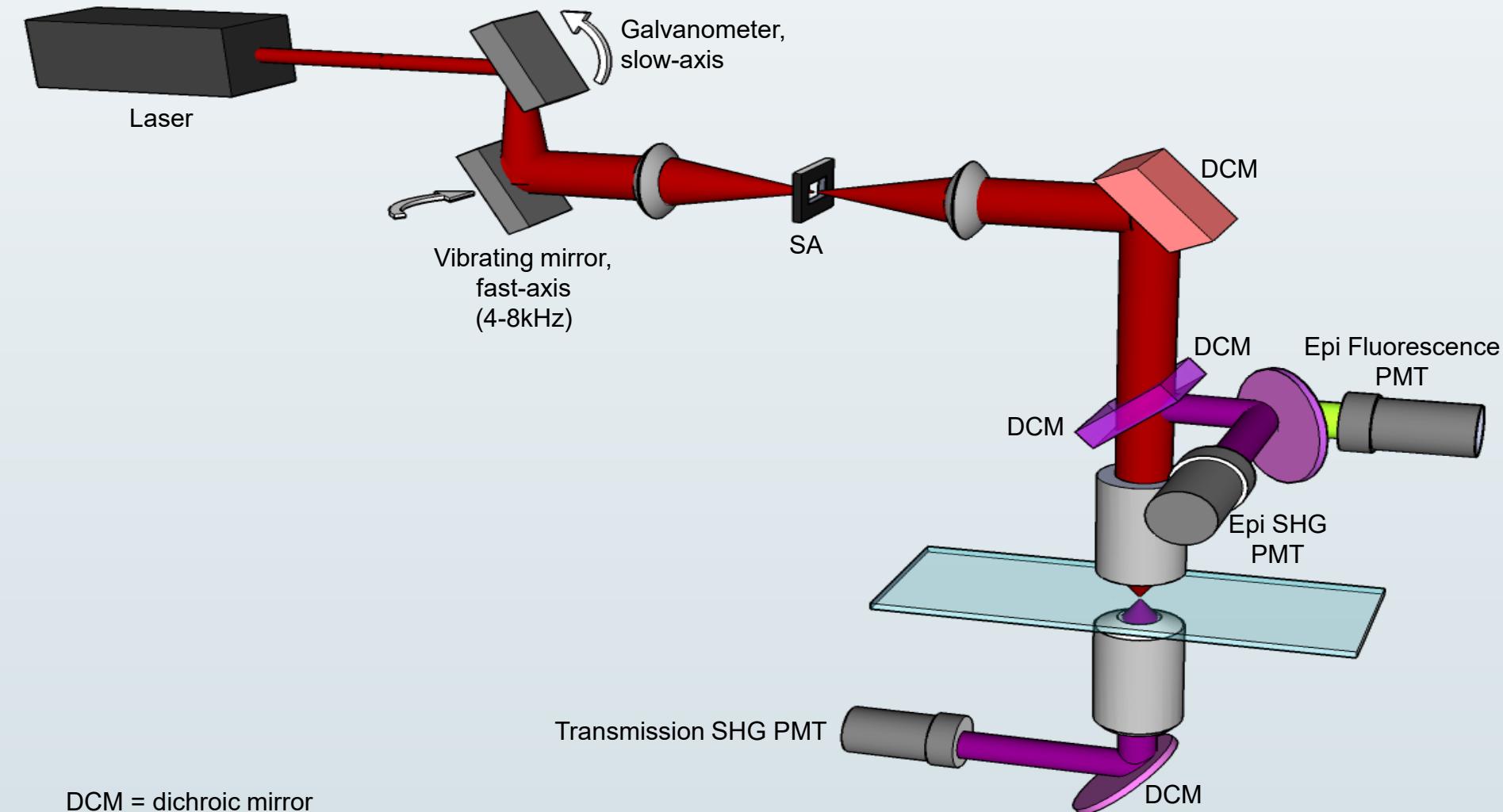


Applicability to APIs

- SONICC: Second Order Nonlinear Optical Imaging of Chiral Crystals
- SONICC can be applied towards the selective and sensitive detection of chiral APIs
 - Most chiral crystals result in space-groups that allow for the occurrence of the SHG phenomena
 - Achiral materials typically result in the formation of centrosymmetric space-groups
 - Detection of twice the incident frequency (1/2 incident wavelength)



The SONICC Instrument

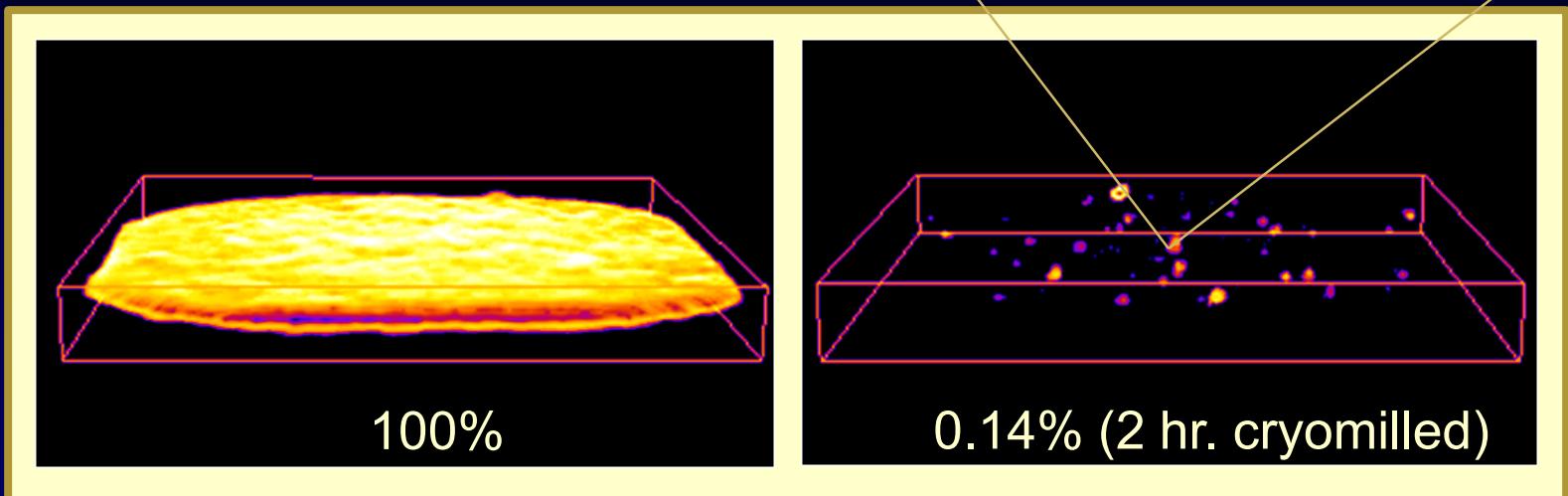
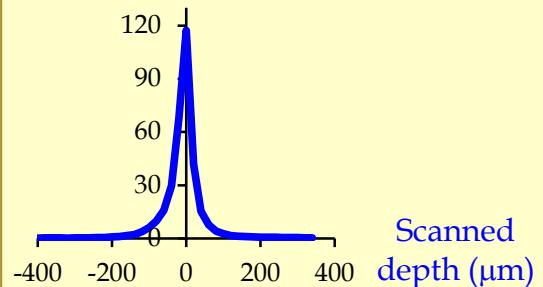


DCM = dichroic mirror
SA = square aperture

SHG Within Cryomilled Griseofulvin

Macroscopic crystallinity
arises from localized
crystalline domains

SHG ($\times 10^4$ counts/sec)



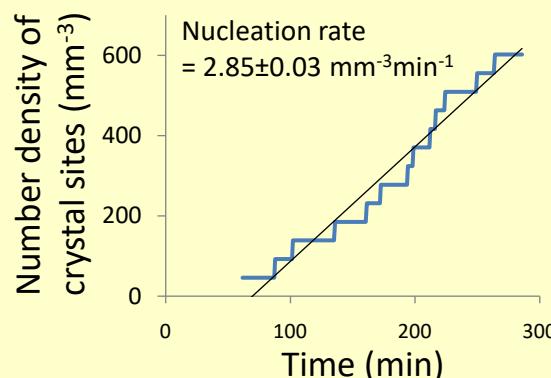
Crystallization Kinetics (Griseofulvin)

Isothermal nucleation

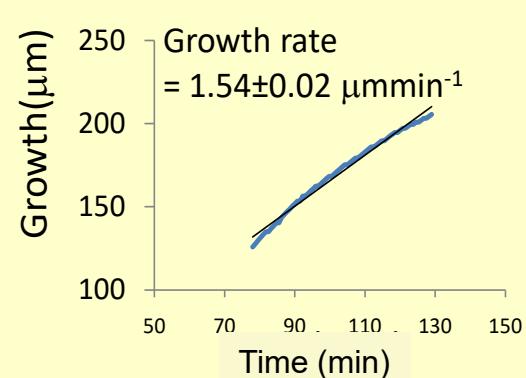


Time

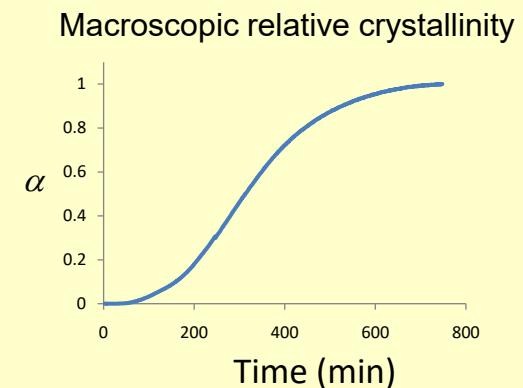
Nucleation rate



Single crystal growth rate



Ensemble average





Goal

- Potential applications
 - API distribution within final dosage forms
 - Anti-counterfeiting
 - Failed final dosage form
 - Ritonavir
 - Shelf life
- Potential obstacle
 - Chiral excipients



Conventional SONICC Measurements

Excipient	Percentages Relative to Griseofulvin		
	Conventional SONICC	TPEF	Combined IR
Griseofulvin (API)	100	100	100
Anhydrous lactose	12.0 ± 0.2	4±1	0.48
Lactose Monohydrate	8.53±0.07	1.45±0.05	0.12
Placebo Mixture 1	0±1.3	1.8±0.4	9.0x10 ⁻³
Placebo Mixture 2	0.5±0.3	2.8±0.2	0.013
Mannitol	0.6±0.1	1.28±0.05	7.2x10 ⁻³
Avicel	0±0.2	2.57±0.03	2.0x10 ⁻³
Opadry® White	0.11±0.02	4.45±0.05	4.8x10 ⁻³
Vitamin E TPGS, HPC, SLS, PVP, HPMCAS- LF, magnesium stearate, A-TAB, Kollidon VA64, colloidal SiO ₂	≤0.020	--	--



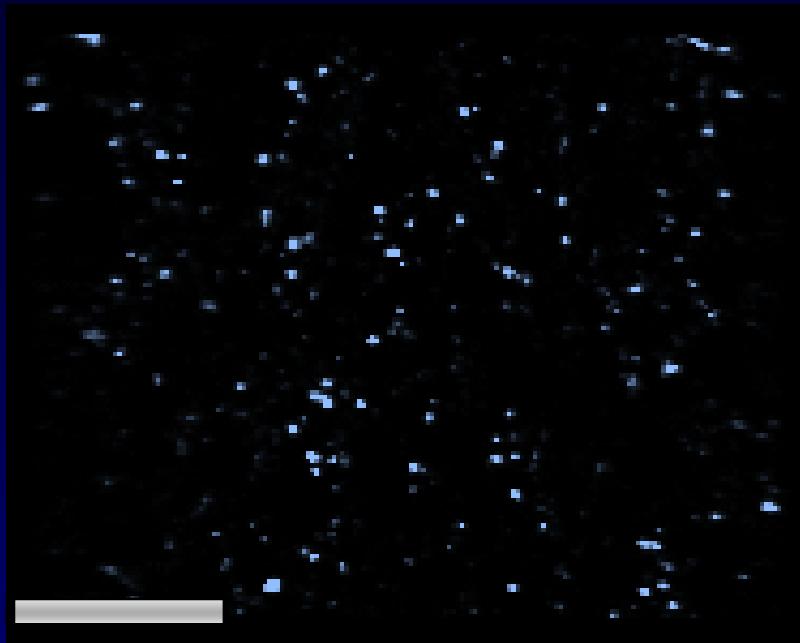
UV-SONICC/TPE-UVF Overview

- 1064 nm laser doubled to 532 nm
- Collecting 266 nm
- TPE-UVF filter ~300-450 nm
- Benefits:
 - Discrimination between SHG-producing excipients and chiral, noncentrosymmetric, aromatic APIs (>75% of APIs)
- Solar-blind PMT, UV collection objective, LBO crystal

2D Intensity Comparison of API

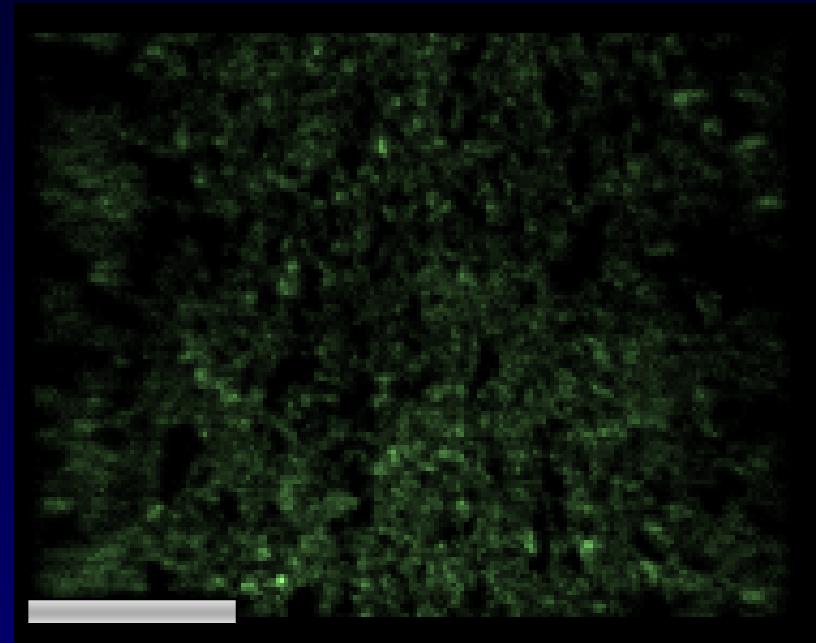
- Powdered griseofulvin
- 10 μm Z step sizes

UV-SONICC



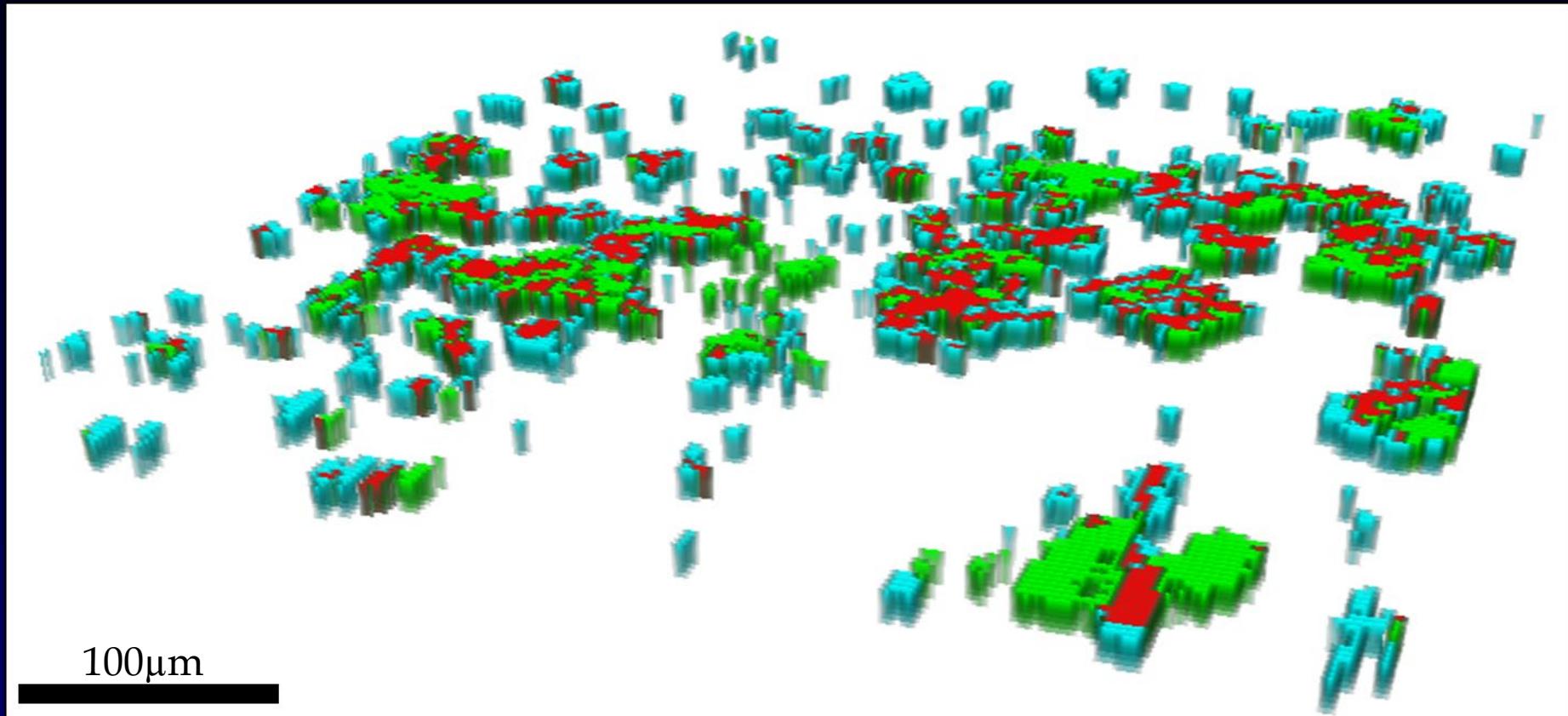
100 μm

TPE-UVF



Surface

Griseofulvin TPE-UVF/UV-SONICC Overlay



100μm



UV-SONICC/TPE-UVF Analysis

Excipient	Percentages Relative to Griseofulvin			
	Conventional SONICC	UV- SONICC	TPE-UVF	Combined UV
Griseofulvin (API)	100	100	100	100
Anhydrous lactose	12.0 ± 0.2	2.1±0.9	0±4.2	8.2x10 ⁻³
Lactose Monohydrate	8.53±0.07	1.0±0.3	0±0.7	4.2x10 ⁻⁵
Placebo Mixture 1	0±1.3	0±1.5	0±2.0	1.4x10 ⁻⁴
Placebo Mixture 2	0.5±0.3	0±1.3	0±0.1	2.0x10 ⁻⁵
Mannitol	0.6±0.1	0±0.7	0±0.9	7.8x10 ⁻⁶
Avicel	0±0.2	0±0.4	0±0.7	7.3x10 ⁻⁶
Opadry® White	0.11±0.02	0±1.3	11±3	2.3x10 ⁻⁴
Vitamin E TPGS, HPC, SLS, PVP, HPMCAS-LF, magnesium stearate, A-TAB, Kollidon VA64, colloidal SiO ₂	≤0.020	--	--	--



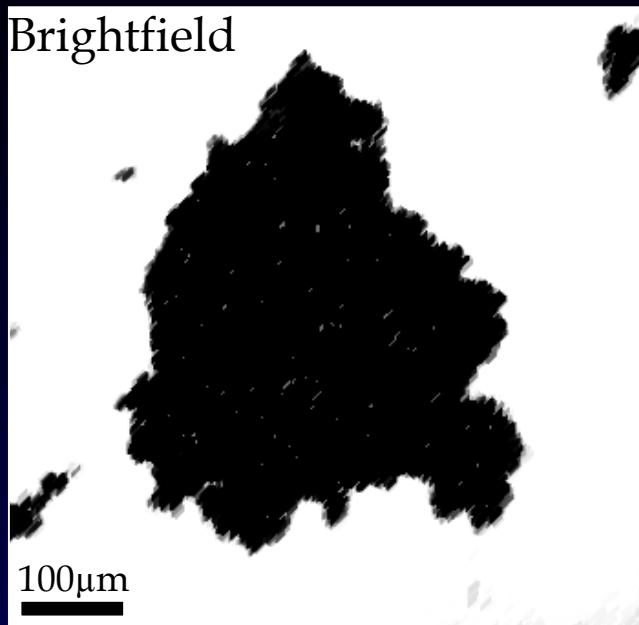
UV-SONICC/TPE-UVF Summary

- The combination of the previously mentioned techniques allow for API/excipient discrimination
 - Granted certain API criteria are met:
 - Chiral/noncentrosymmetric
 - Aromatic (>75%)
- ~3 orders of magnitude reduction in background

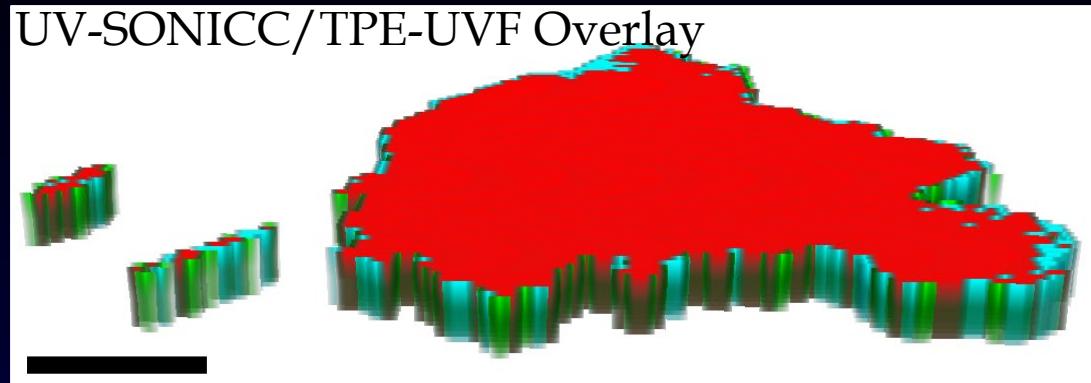


Imaging Final Dosage Forms

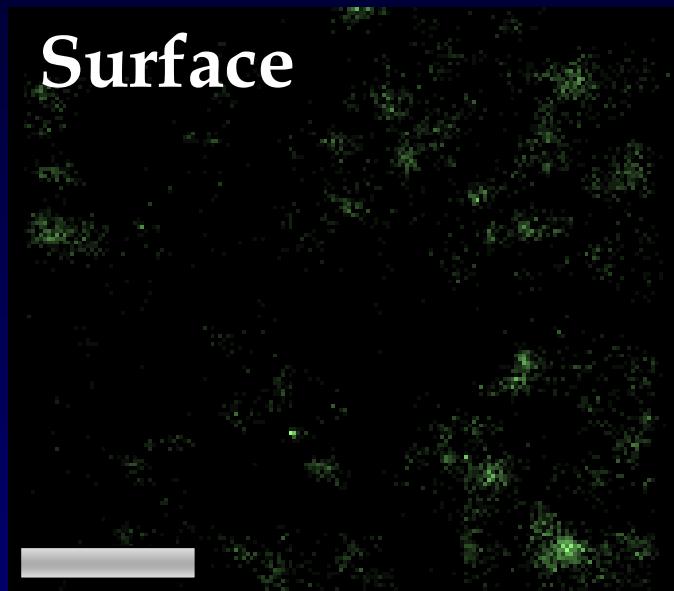
Brightfield



UV-SONICC/TPE-UVF Overlay



Surface



□ Cialis®, with the API tadalafil



Conclusions/Future Work

- ❑ Enhance ability to probe further into final dosage forms
- ❑ Chirality/polymorph detection
- ❑ Counterfeit detection with SONICC

Acknowledgements

- The Simpson Group
- Purdue University
 - Department of Chemistry
 - Department of Physical and Industrial Pharmacy
 - Lynne Taylor
 - Umesh Kestur
 - JAFCI
- Merck
- Funding:
 - NIH, Dane O. Kildsig Center of Pharmaceutical Processing Research

