Analytical Approach to Investigate Salt Disproportionation in Tablet Matrices by Stimulated Raman Scattering Microscopy

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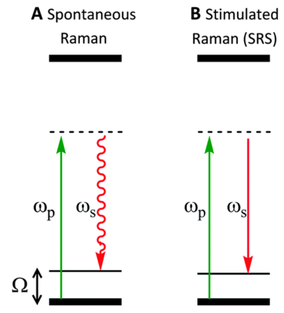
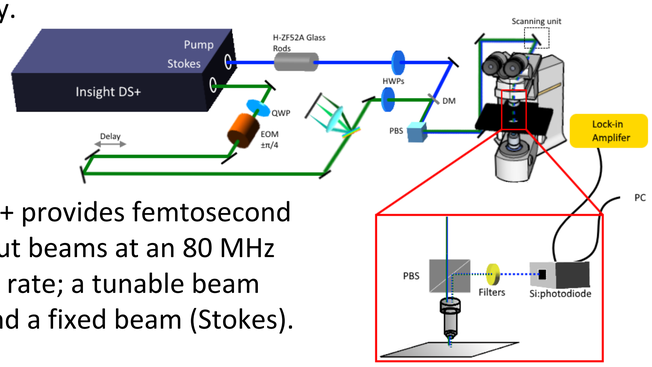
Background

Within drug tablets, it is known that salt disproportionation could affect the stability and bioavailability of the active pharmaceutical ingredient (API), thus hindering the drug's effectiveness. We employ stimulated Raman scattering (SRS) microscopy to analyze salt disproportionation within a tablet matrix. Salt disproportionation describes the conversion from its active salt form (PIO-HCl) to the inactive free base form (PIO-FB). We aim to detect and quantify changes in a model drug system, Pioglitazone and deuterated Magnesium Stearate.

SRS technique

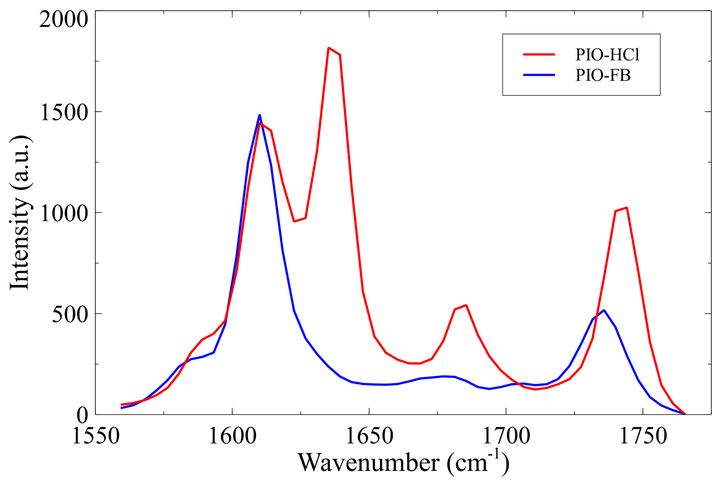
Label-free chemical contrast is highly desirable in biomedical imaging. Vibrational spectroscopy techniques such as Spontaneous Raman microscopy provides label-free chemical imaging, however it suffers from slow acquisition rates, poor spatial resolution, and lack of sensitivity. SRS is a nonlinear technique which coherently excites a Raman vibration, improving signal for fast imaging speed and high sensitivity.

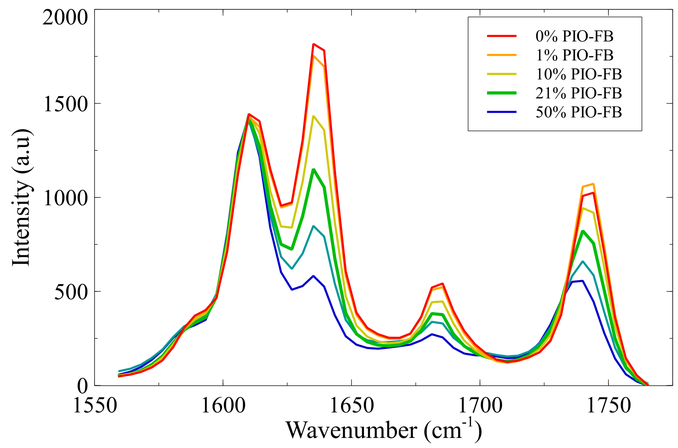




Insight DS+ provides femtosecond dual output beams at an 80 MHz repetition rate; a tunable beam (Pump) and a fixed beam (Stokes).

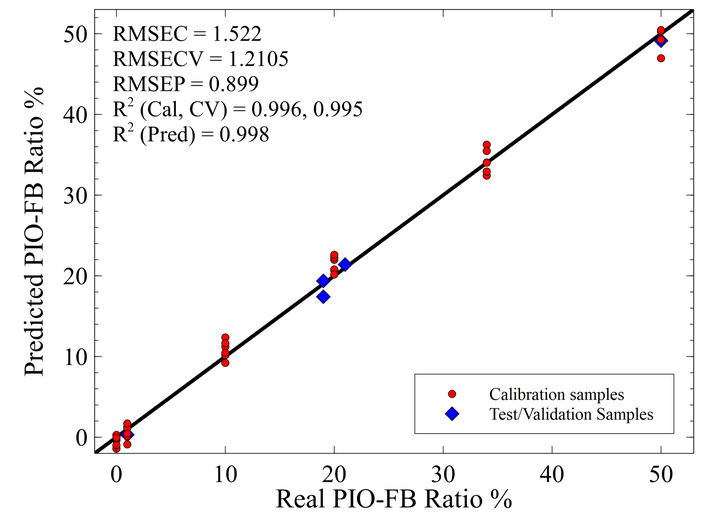
SRS spectra of Pioglitazone



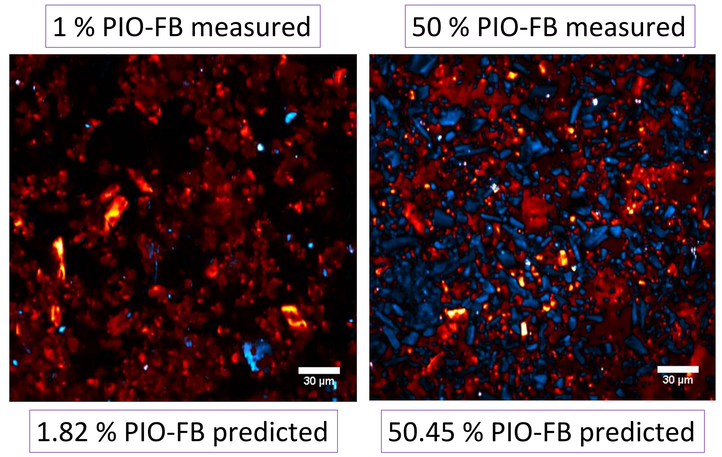


Calibration and Regression

Partial Least Squares (PLS) was the multivariate regression method used to build quantitative calibration models. Samples were prepared for generating a calibration curve ranging from 100% PIO-HCl (0% PIO-FB) to 50% PIO-HCL (50% PIO-FB). Each calibration standard was scanned 6 times with the SRS system. A PLS model was built and tested with new samples for prediction.

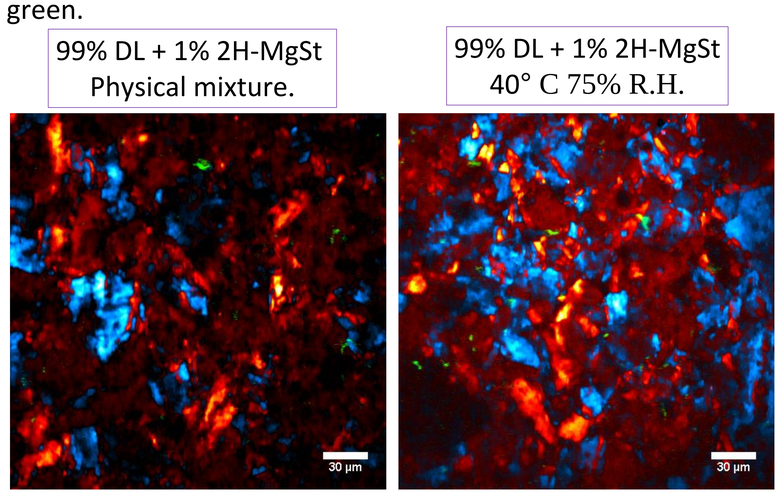


Chemical Images (powder)



Chemical Images (tablet)

Mgst has been known to be an excipient that accelerates the rate of disproportionation within a tablet. Mgst is a proton acceptor and convert PIO-HCl to its free base form. Additionally, Mgst is a hygroscopic ingredient, which could lead to the presence of water in the tablet which will promote the salt disproportionation reaction, when exposed to high relative humidity conditions. Deuterated Mgst in green.



Outcomes

Preliminary results indicate that SRS could prove useful for the quantification of salt disproportionation at low drug loadings via PLS regression. Differences in SRS spectra can be seen between different methods of sample preparation. Caution must be taken into account when building PLS models for different preparation methods.

Future Directions

We will employ SRS to tablets with low drug loading (1%) and apply PLS models to quantify the amount of PIO-FB to PIO-HCl within a multicomponent tablet matrix. This label-free chemical imaging tool will help formulation scientists detect and understand salt disproportionation and *in situ* drug-excipients compatibility issues in low dose solid dosage formulations.

Thanks!

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