Coupling Chemical Analysis to High Resolution Microscopy for Enhanced Physicochemical Characterization of Drug Products Containing Nanomaterials and Other Complex Formulations

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Introduction

Drug products containing nanomaterials have increased in prominence as submissions to the FDA. Many of these newer drugs are complex dosage forms containing particles in single or multi-phasic systems. Oftentimes, the actual microstructure of the product is unknown. As the number of products increase, so do the questions on how to appropriately define and characterize the critical quality attributes of these formulations. Analysis of the particle size distribution (a common characterization for these types of products), either through light scattering or imaging, is rarely able to provide information concerning the chemical microstructure of the drug product (e.g. the location of the Active Pharmaceutical Ingredient (API)). This information becomes more critical from a quality control perspective as the complexity of the formulation increases. The focus of our work, therefore, is to quantitatively evaluate the particle size distribution within complex drug formulations as well as obtain overall microstructural information about the drug products by employing darkfield microscopy with hyperspectral analysis.

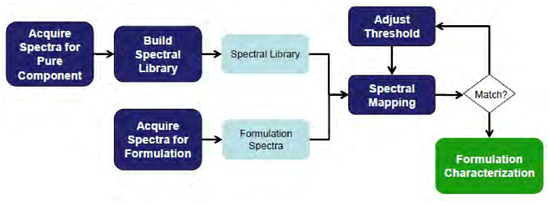
Objectives

- The focus of this project, therefore, is to evaluate high resolution imaging methods that operate under distinct mechanisms to quantitatively evaluate the particle size distribution within complex drug formulations as well as obtain overall microstructural information about the drug products.
- These methods will then be further coupled to additional chemical and phase analyses to provide an enhanced physicochemical characterization of the drug product.

Methods

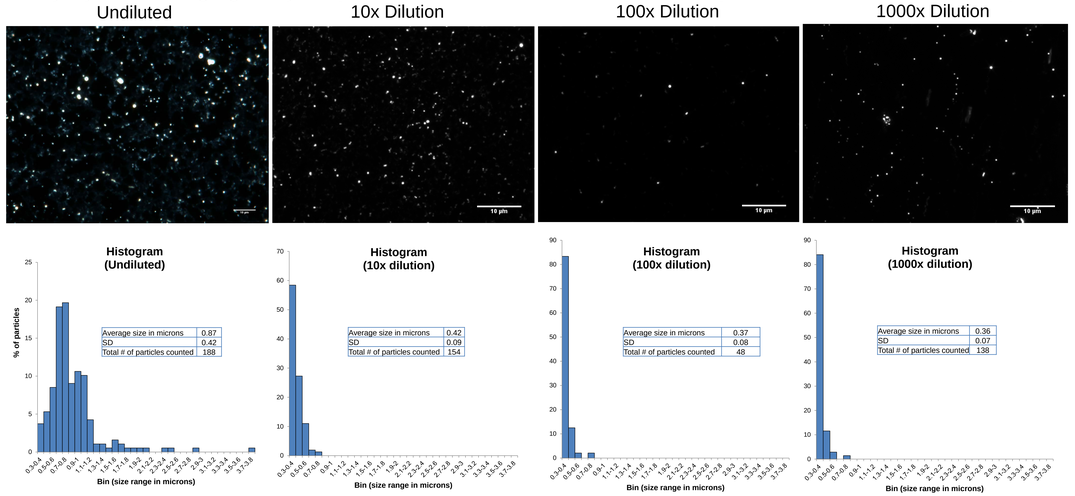
- Select marketed emulsions and creams were mounted directly on a glass slide with a coverslip.
- The CytoViva® microscope system was adopted to acquire darkfield microscopy images and hyperspectral plots using an enhanced darkfield transmission optical microscope (Olympus BX41) equipped with a CytoViva® unit (CytoViva®) and a hyperspectral imaging spectrophotometer unit (Headwall Photonics).
- CytoViva can measure small features that standard optical imaging techniques cannot by improving the alignment and focus of illumination and enhancing the signal-to-noise of nanoscale materials. The particle size distribution of the formulations was determined by ImageJ analysis of the captured optical images.
- This system is also capable of recording high quality spectra (high signal-to-noise ratio) in the visible and near infrared wavelength range (400-1000 nm). Hyperspectral images were acquired using a 0.5 s collection time and a halogen light source. Images were acquired using a 100x oil immersion lens.
- Qualitative hyperspectral analysis of the acquired images was performed using ENVI 4.8. Spectral libraries were built with known pure chemical components of the formulations and then applied to unmodified formulated products to obtain an image of their chemical microstructure.

Mapping Analysis Workflow



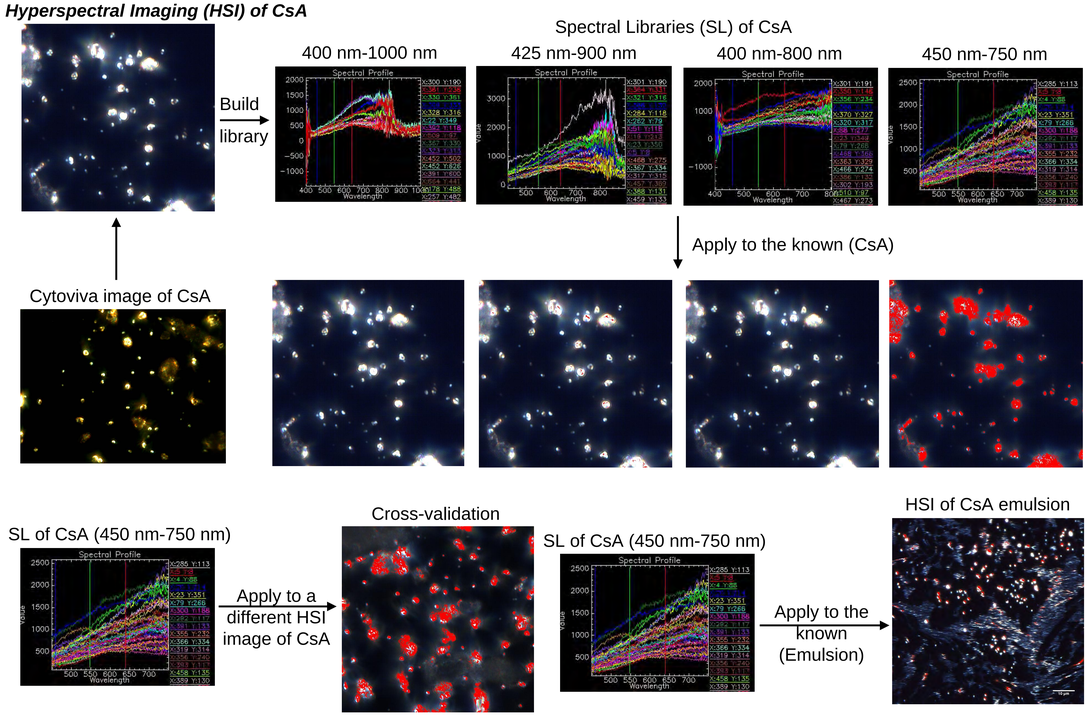
Results

Size by CytoViva Imaging of Cyclosporine Ophthalmic Emulsion (100X): Impact of Dilution in Sample Preparation



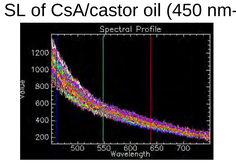
Hyperspectral Mapping/Matching (100X)

Hyperspectral Imaging (HSI) of CsA



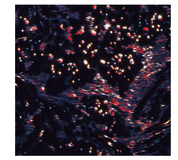
Results continued

SL of CsA/castor oil (450 nm-750 nm)

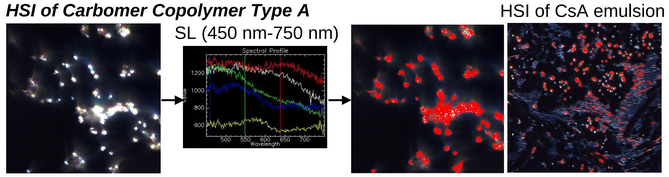


Apply to the known (Emulsion)

HSI of CsA emulsion



HSI of Carbomer Copolymer Type A



Discussion

- The enhanced darkfield optical illumination system allowed the observation of the polydispersity of nanoscale domains within the complex formulations and provided complementary results to the measurements obtained by DLS. By applying CytoViva® microscopy to a multi-modal formulation, the different size populations were identified (similar to the DLS histograms), but image analysis was further able to distinguish agglomerates, which is not possible with light scattering techniques.
- By constructing spectral libraries of reference materials, this method allowed for the identification and mapping of nanoscale domains within an oil-in-water emulsion. We were able to distinguish and discriminate the liquid microenvironments in multiphase formulations as well as identify the distribution of the API within the drug product. We were also able to optically and spectrally analyze other complex environments such as a cream.
- This report demonstrates proof-of-concept data using this imaging technique to establish the location of the API in a complex microstructure. Further work includes method validation and technique robustness evaluation.

Conclusions

- By coupling chemical information with morphological information arising from high resolution imaging techniques, we can redefine the role of imaging methods in the characterization of complex drug products by capturing key information about the microstructure of the formulation that otherwise would not be able to be obtained.
- Determination of imaging parameters for quality controls and physicochemical characterization will support research in nanotechnology and development of complex drug products. In addition, the project will provide a framework for robustness studies when validating imaging methods for complex products.
- Finally, specific questions about the morphology of complex formulations of interest will be addressed and would represent an improvement in our ability to understand complex microstructures and the critical quality attributes that govern these drug products.

Acknowledgement and Disclaimer

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