Using Chemical Imaging to Reverse Engineering a Drug Product Matrix

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1. Introduction

The Materials Characterisation Team were requested to perform near-infrared chemical imaging to reverse engineer a drug product matrix.
The project aims were to provide information on the product characteristics to feed back to the development team with potential to produce a viable generic product.

2. Experimental

A 5000 µm by 5000 µm sample area of each tablet was examined using the near-infrared microscope. The resultant dataset was treated with Partial Least Squares regression against a known library of components.

3. RGB Images

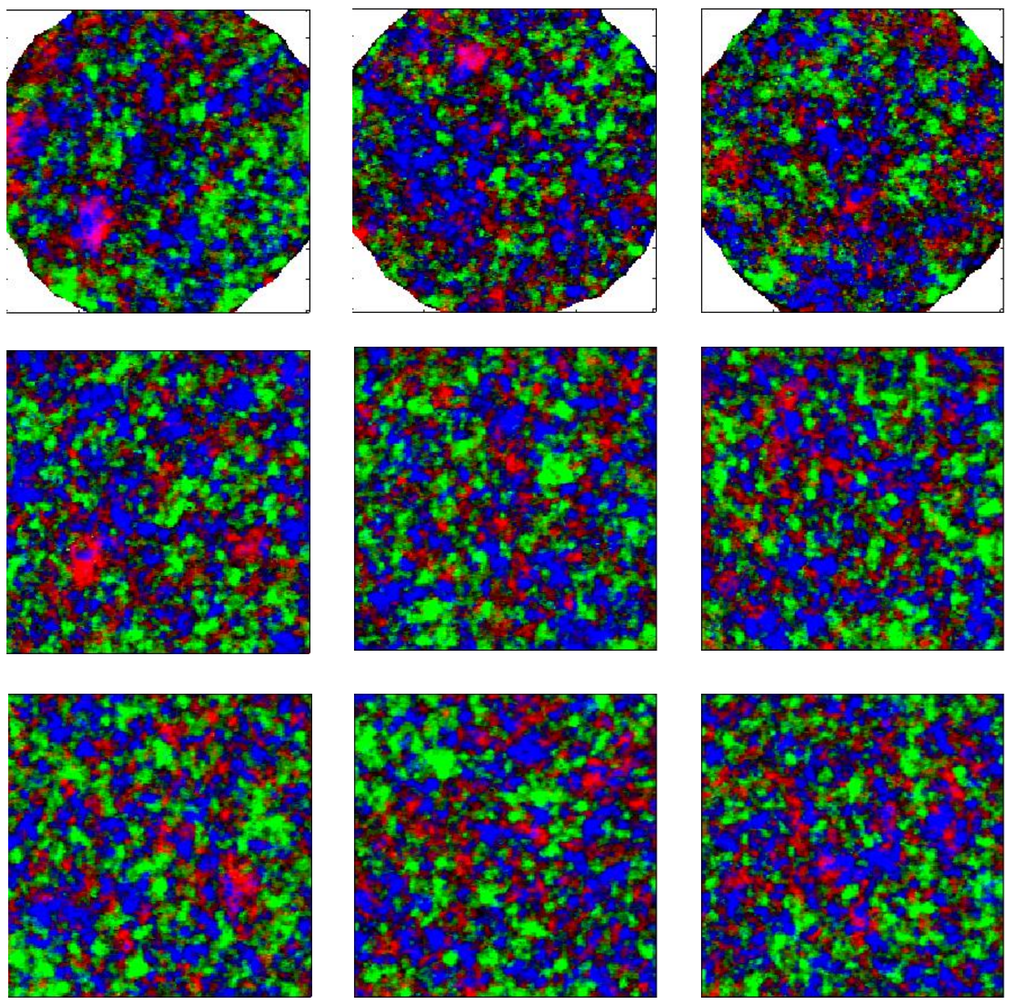

Figure 1. RGB images of 20 mg (top), 80 mg (middle) and 140 mg (bottom) strength where red = API A, blue = excipient A and green = excipient B.

The 80 mg and 140 mg strength show very similar homogenous distribution of the active drug throughout which is consistent with a wet granulation process. The 20 mg tablets appear to be less homogenously distributed.

4. Raman Mapping

Raman mapping was performed to confirm formulation details and determine any unidentified components.

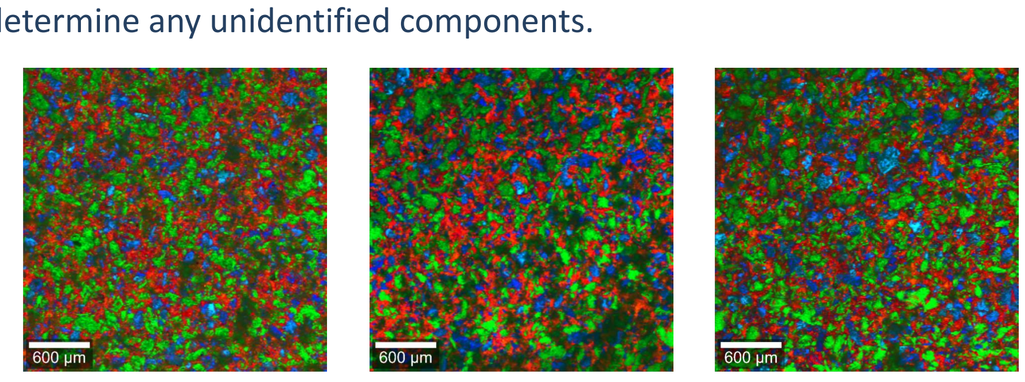

Figure 3. Raman Maps of 20 mg (left), 80 mg (middle) and 140 mg (right) strength where red = API A, blue = excipient A and green = excipient B.

These maps are similar to the near-infrared chemical images and identify no further components.
A Spectrum was collected from four 'API rich' regions in each tablet and compared with a spectrum of the monohydrate form of the API.

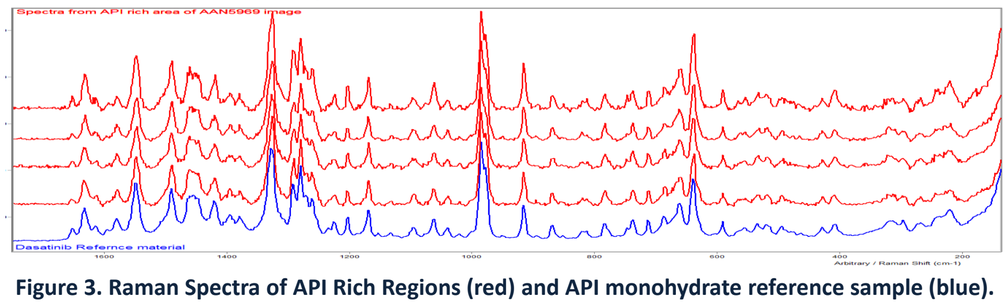

Figure 3. Raman Spectra of API Rich Regions (red) and API monohydrate reference sample (blue).

The spectra from of all the API regions in the tablet is consistent with the monohydrate form and confirms that this is the polymorphic form in the formulation.

5. Pixel Distributions

To objectively determine the distribution of components within the tablet matrix, pixel distributions obtained from the Partial Least Squares Regression analysis are shown below. These distributions can be used to predict the concentration of the component within the tablet matrix and assess the distribution across the tablet image.

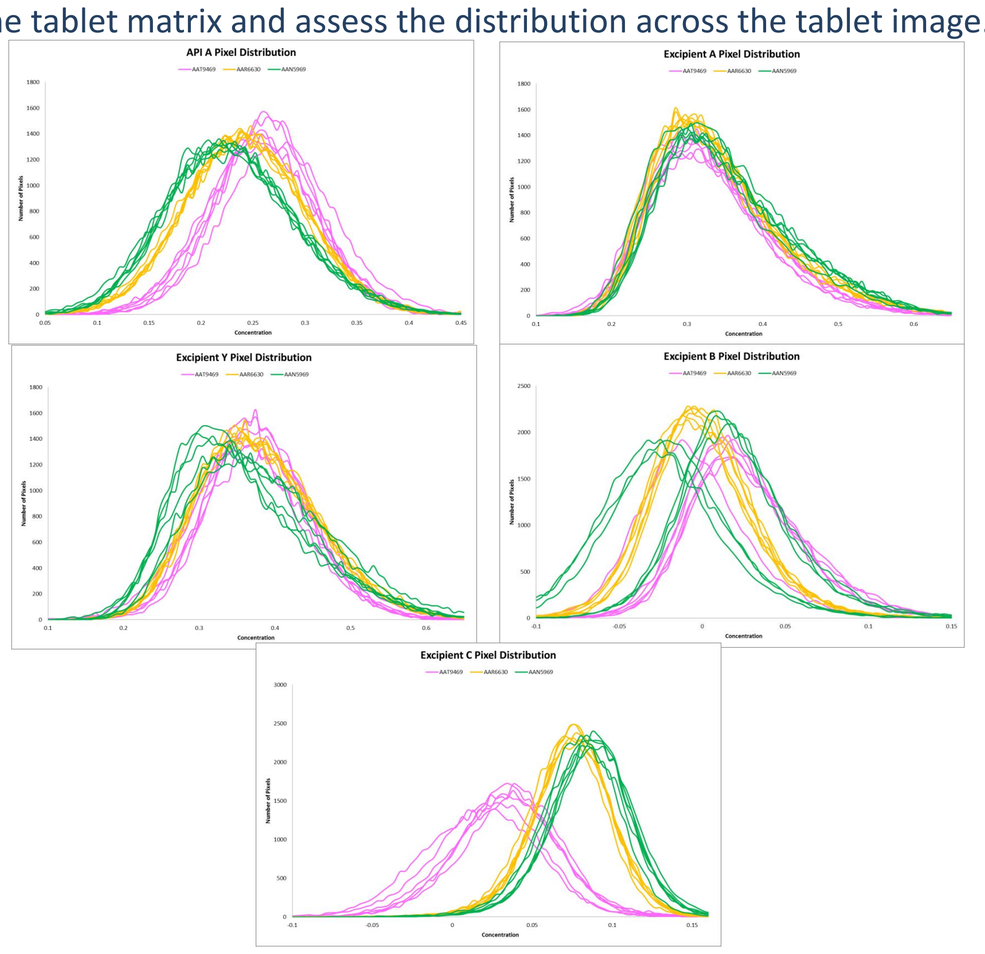

Figure 2. Pixel Distributions of each component for 20 mg (pink), 80 mg (orange) and 140 mg (green)

- There is a difference in the peak max of the distributions of API A suggesting the three strengths have different concentrations of this component.
- There appears to be no difference for excipient A and only a small difference for excipient Y.
- There is variability in the smaller concentration components, however commonly it is difficult to resolve lower level components in a wet granulation process.

The predicted concentration of each component is provided below.

Material	20 mg	80 mg	140 mg
API A	25.9	24.4	22.8
Excipient A	33.7	33.7	35.1
Excipient Y	37.8	38.2	38
Excipient B	2.4	0.5	2.1
Excipient C	3.5	7.7	8.1
Excipient D	n.d.	n.d	n.d
Total	103.3	104.5	106.1

Table 1. Formulation prediction calculated from PLS Squares Regression Analysis

The predicted percentage formulation exceeds 100% which cannot be accurate. This is due to the requirement to classify image pixels to one chemical class. This is a difficult step in analysis and can lead to over or underestimation of a material.

6. Conclusion

Reverse engineering this drug product has revealed some key properties. The distribution of components is consistent with a wet granulation process. The formulation composition has also been predicted.