

Distribution Analysis of Components in the EVRA® Patch by Confocal Raman Microscopy



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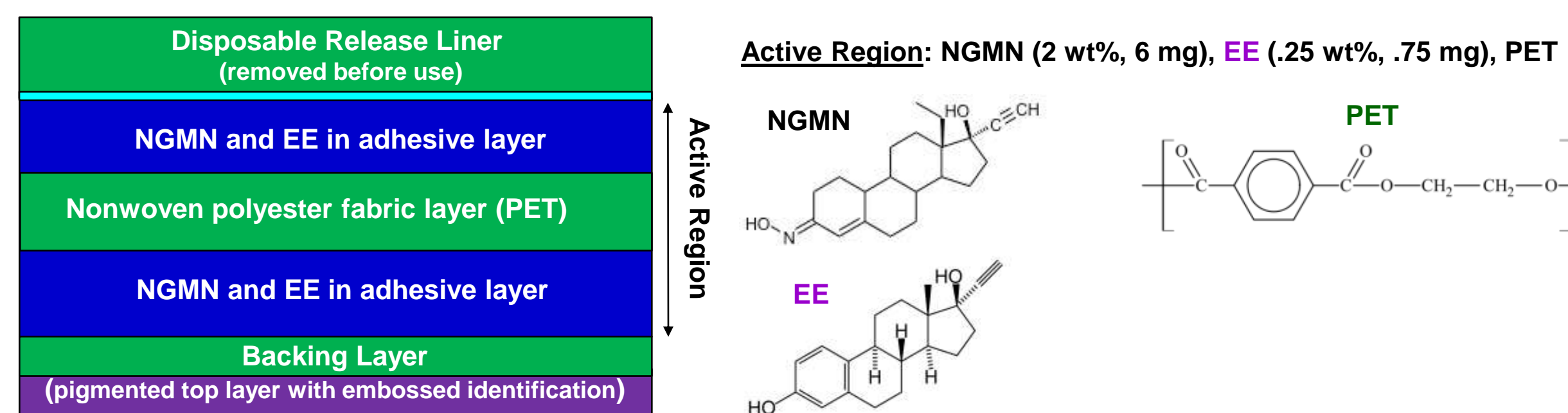
Introduction

Confocal Raman microscopy (CRM) mapping is a powerful tool for distribution analysis of components within complex matrices. CRM combines the submicron spatial resolution of confocal microscopy with the nondestructive content analysis capabilities of Raman spectroscopy. CRM maps are generated by raster scanning the sample through a focused laser beam and collecting a spectrum at each position. The CRM data is then reconstructed to form an image composed of hundreds to thousands of pixels, each containing a full Raman spectrum.

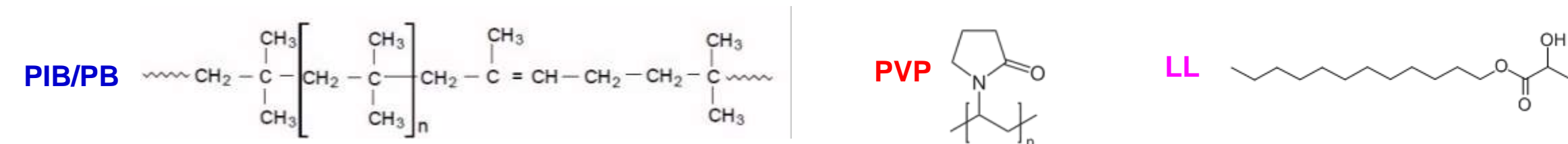
CRM images were generated at different locations within EVRA® samples to characterize drug product and excipient distribution within the adhesive matrix. A set of formulation standards was prepared and analyzed to facilitate PLS modeling. Component distribution analysis was performed on EVRA® patches as a function of time from manufacture through product expiry and a partial least squares (PLS) model was developed to determine if any change in drug concentration relative to PVP concentration occurred.

Background/Experimental

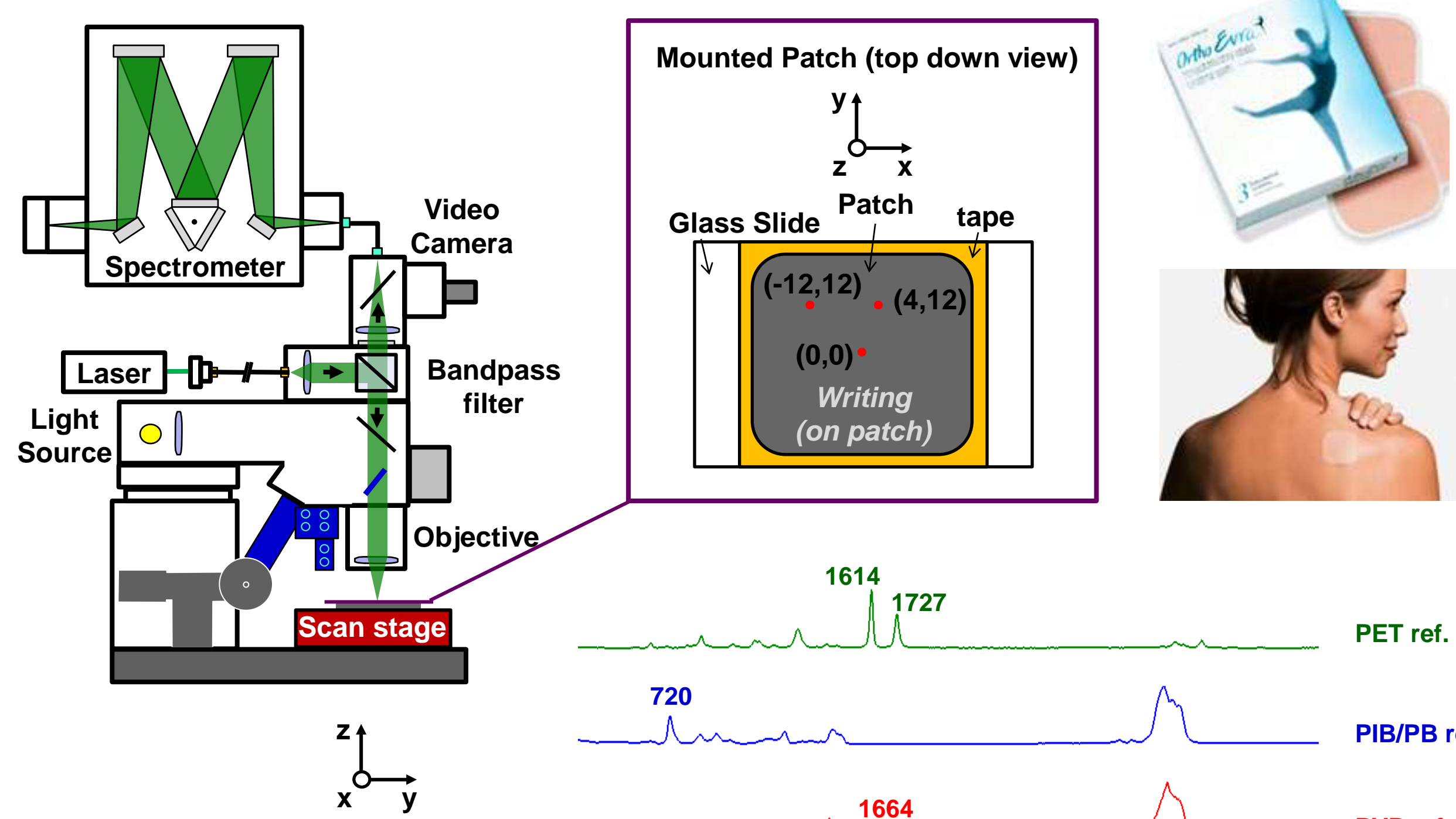
Active region is composed of norelgestromin (NGMN), ethinylestradiol (EE), polyisobutylene/polybutene (PIB/PB), crospovidone (PVP), and lauryl lactate (LL) with nonwoven fibers composed of polyethylene terephthalate (PET)



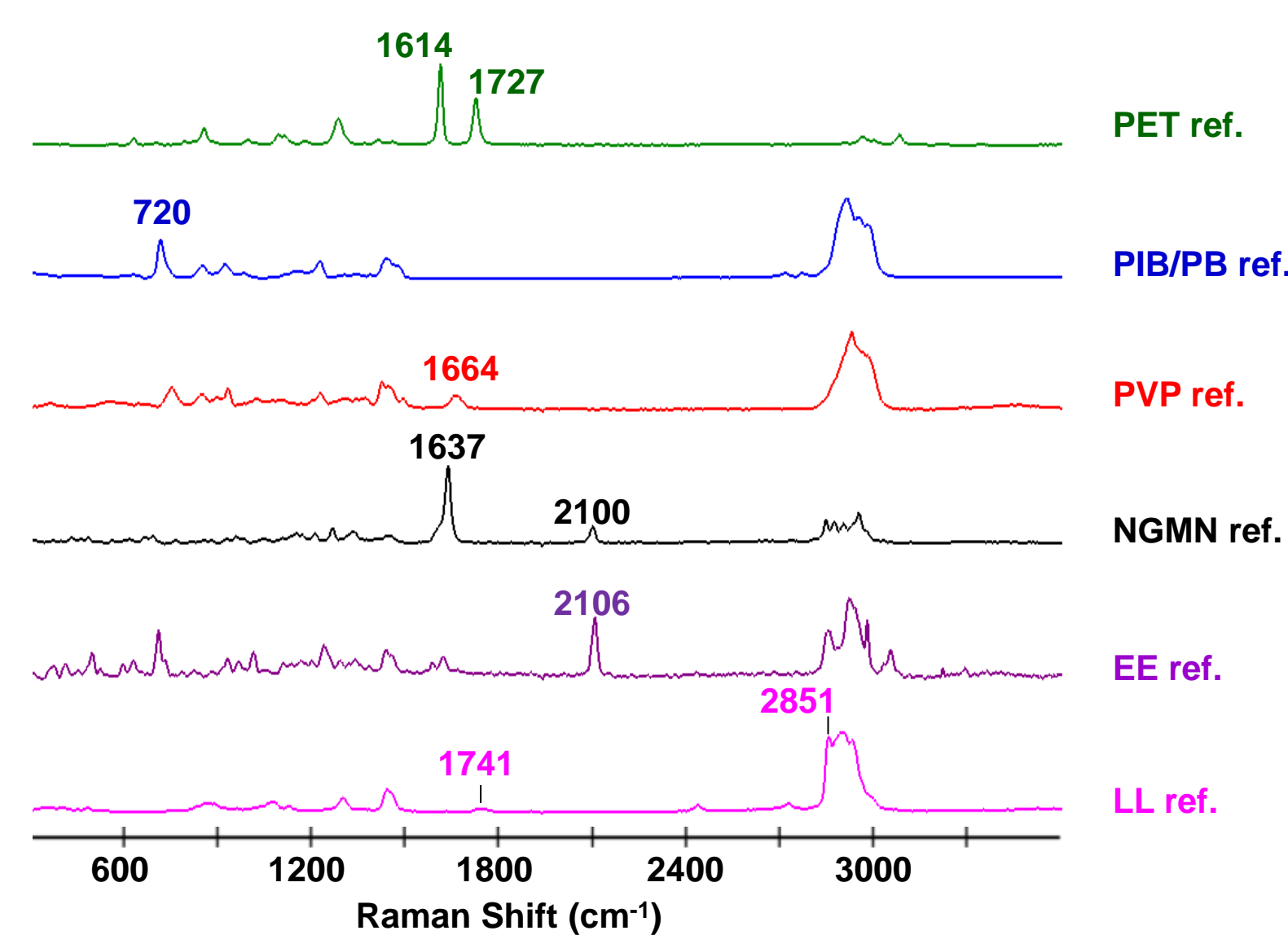
Excipients: PIB/PB (73.75 wt%, 221.25 mg), PVP (20 wt%, 60 mg), LL (4 wt%, 12 mg)



Schematic of CRM experiment showing mounted EVRA® patch

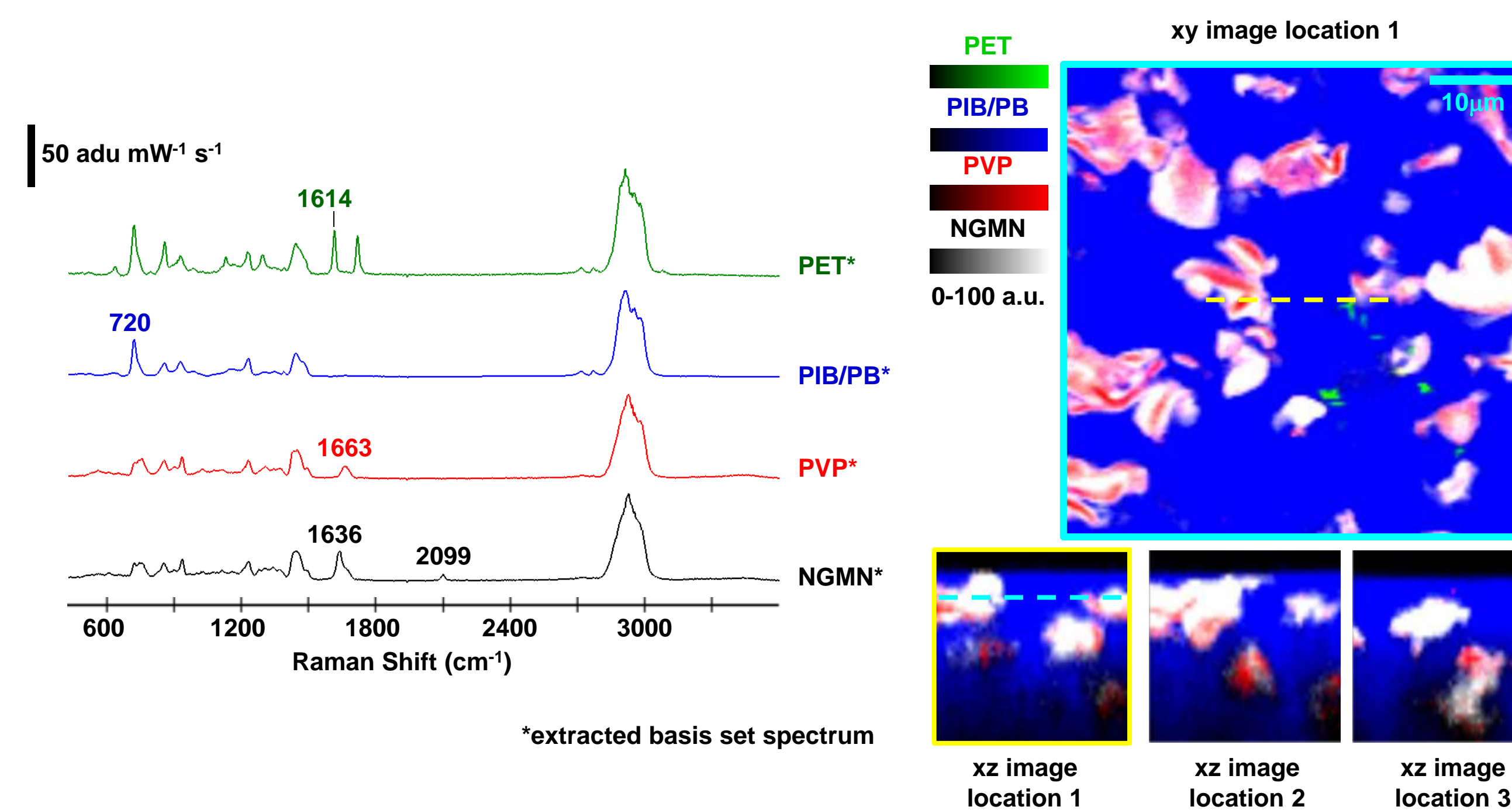


Reference spectra of all components found in active region

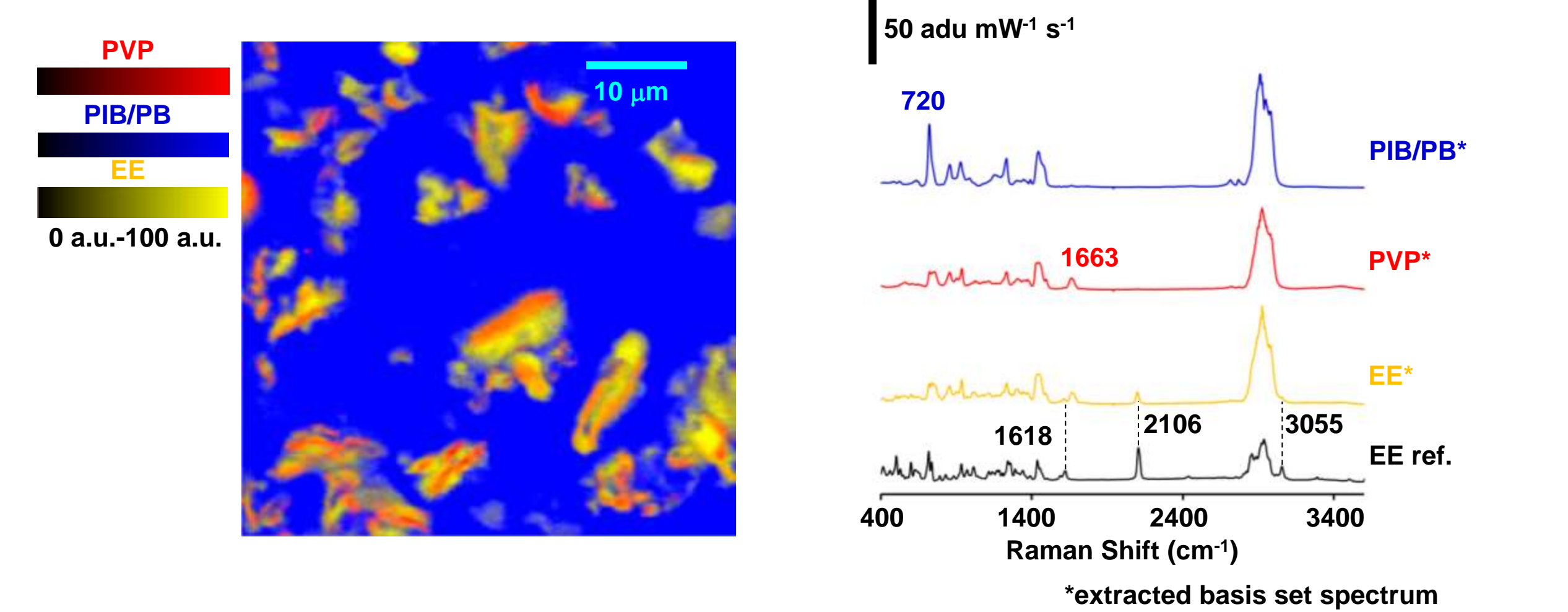


CRM Imaging of EVRA® Patches

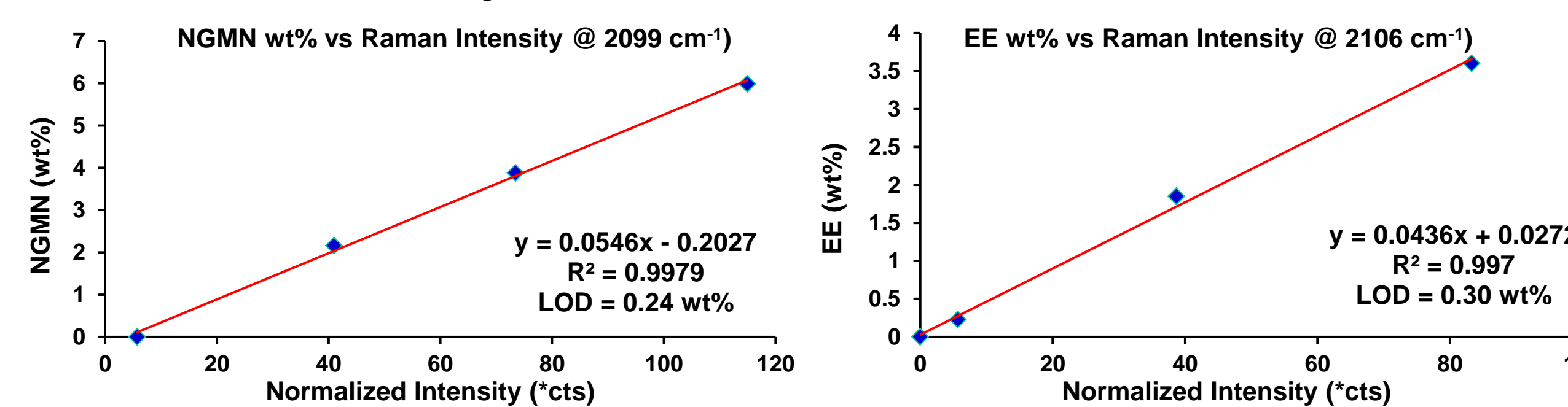
Spectra characteristic of PET, PIB/PB, PVP, and NGMN extracted from CRM image of EVRA® sample



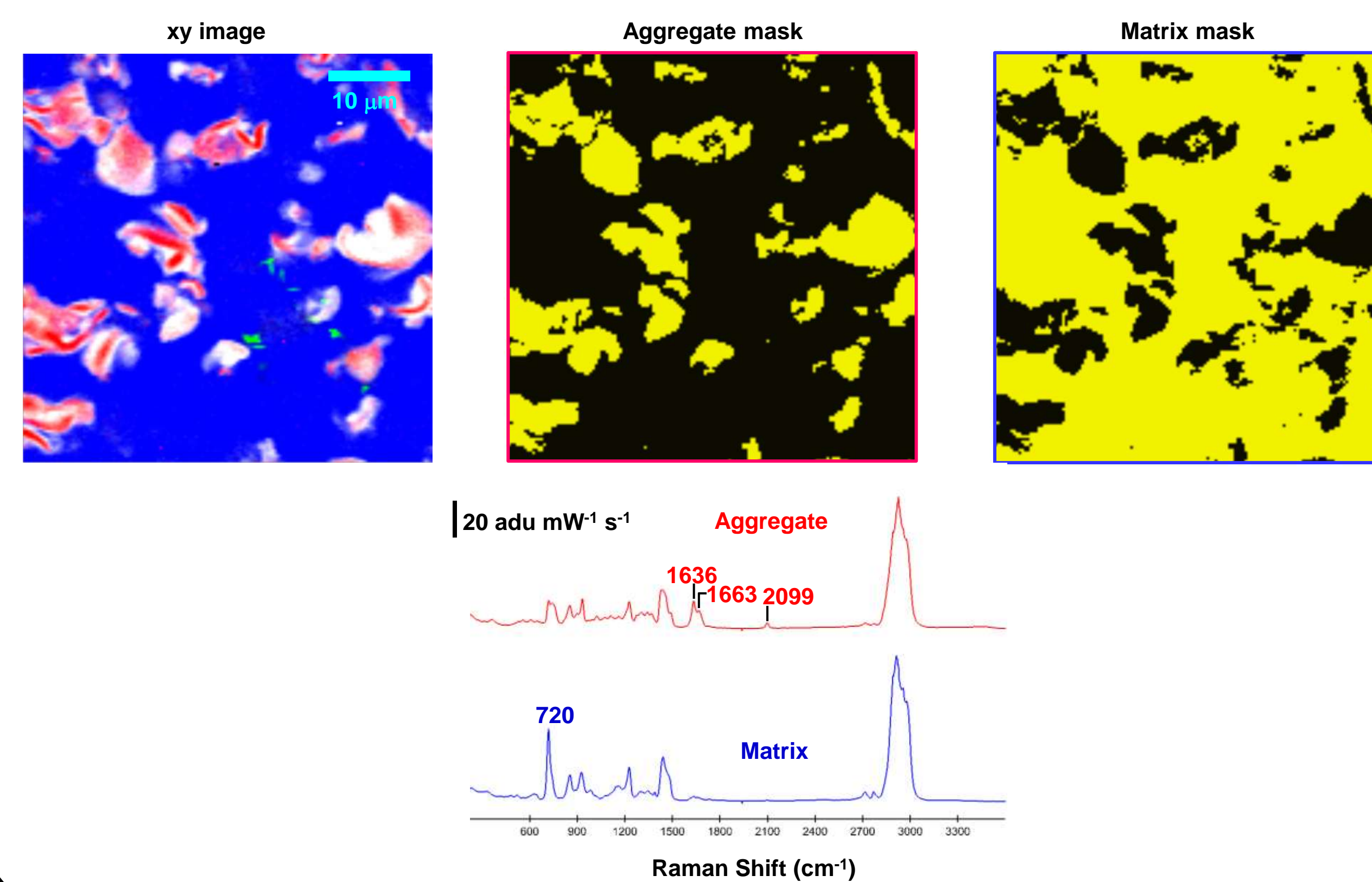
CRM image of an EVRA® formulation standard patch with 4 wt% EE and no NGMN. The CRM image indicates EE concentrates on PVP rich regions just as NGMN does in a nominal EVRA® patch.



NGMN and EE wt% vs intensity using formulation standard patches. Limit of detection (LOD) is defined as concentration at 3 standard deviations above background noise.

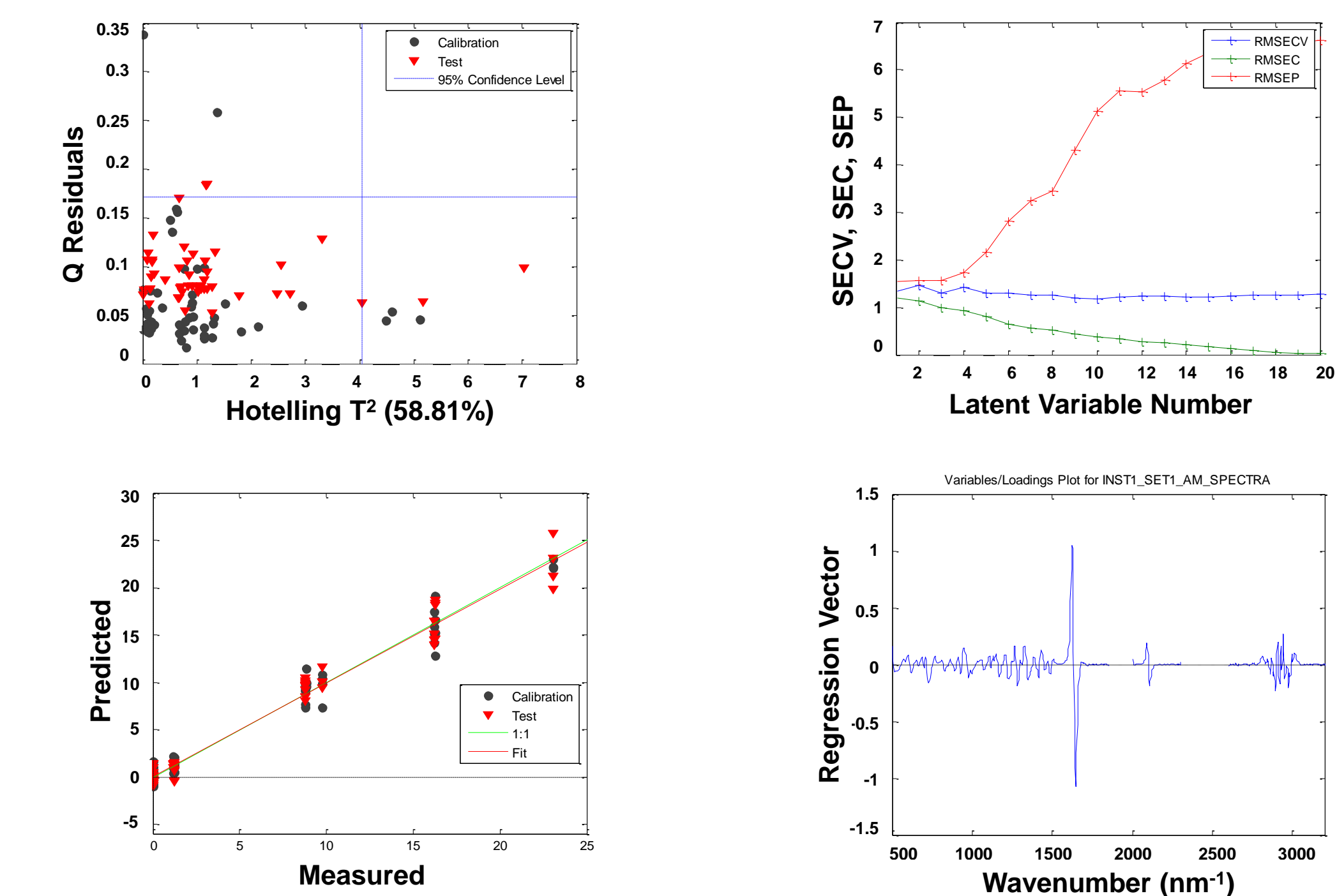


Aggregate and matrix masks generated from the xy image at far left. The average spectra generated from the aggregate (red trace) and matrix (blue trace) masks are shown on right.

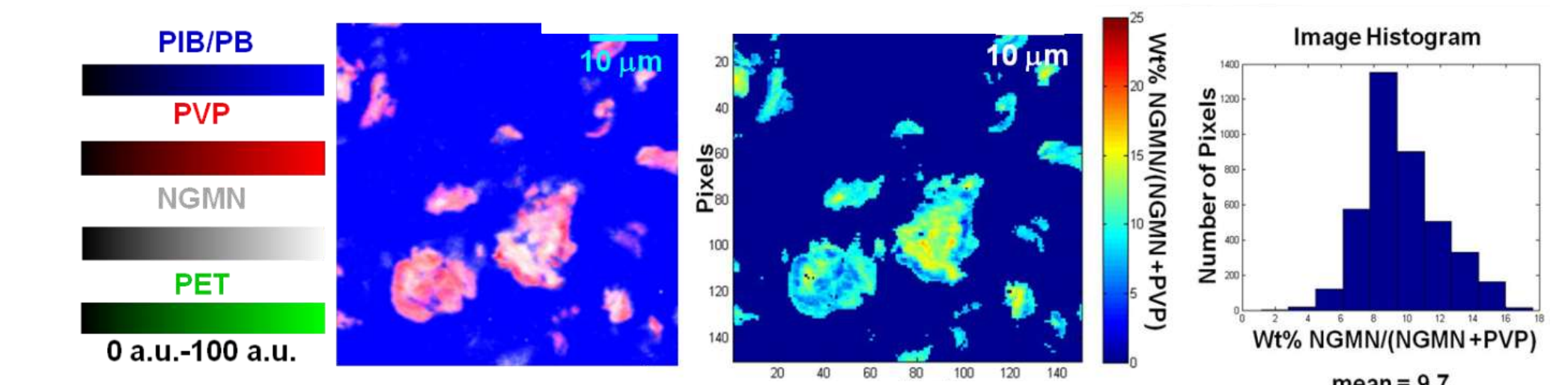


PLS of EVRA® CRM Images

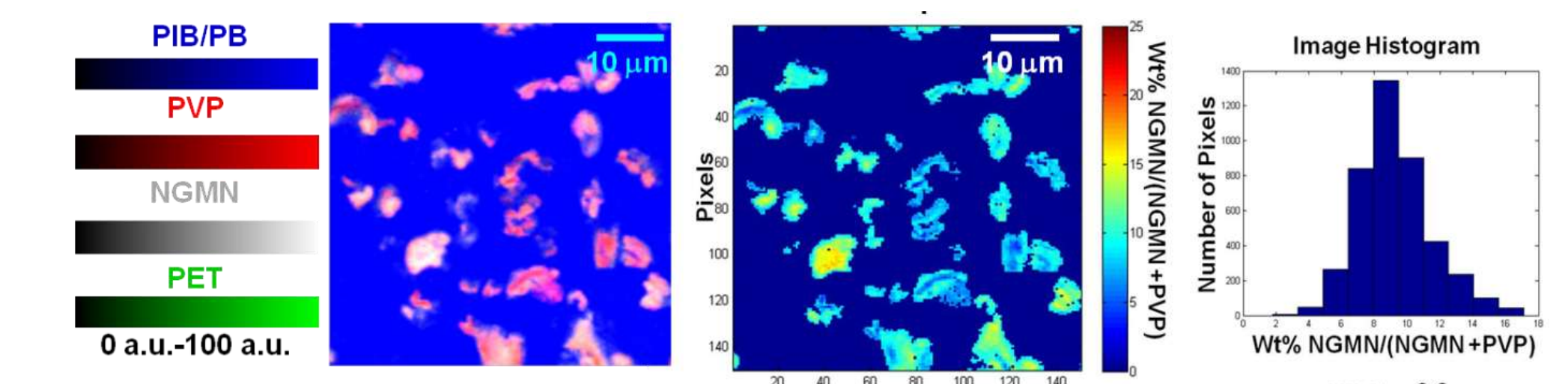
PLS image showing predicted NGMN wt%/(NGMN wt%+PVP wt%)



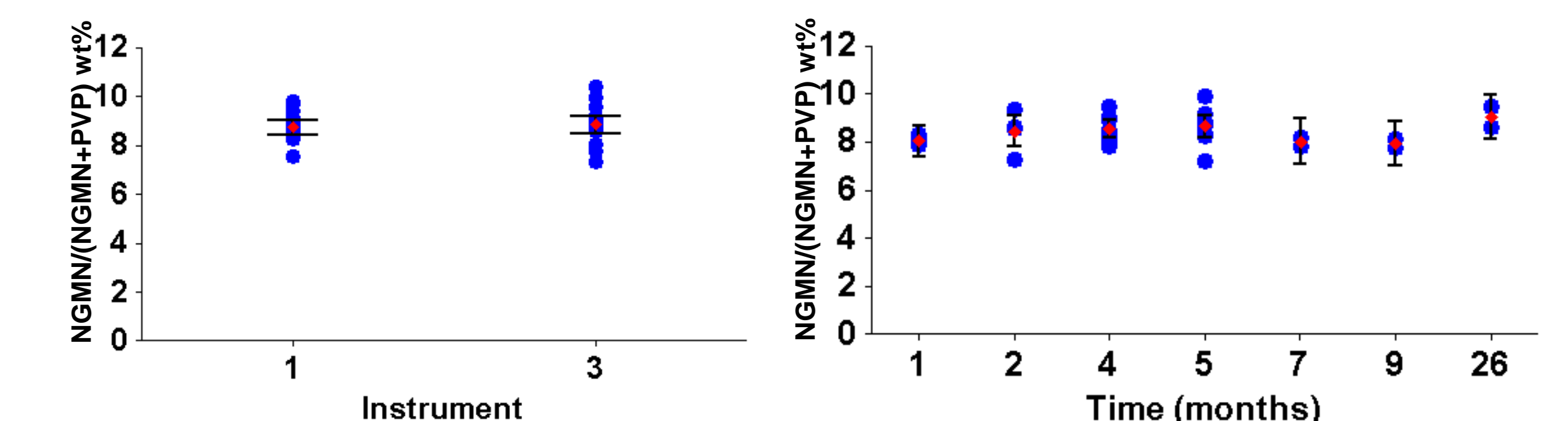
1 Month



7 Month



Instrument Variation



Conclusion

Distribution analysis was performed on all components in the active region of the EVRA® patch

NGMN and EE are strongly associated with PVP aggregates dispersed throughout the adhesive matrix with no NGMN or EE detected in the PIB/PB matrix.

LL associates with both the aggregate and matrix regions within patch

NGMN concentration does not change significantly with respect to PVP concentration from time of manufacture

Acknowledgements

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