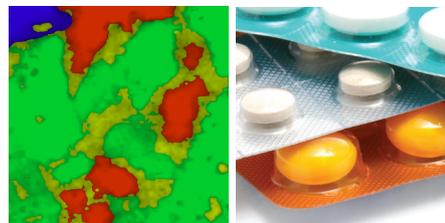


Raman Spectroscopy to Study the Distribution of Compounds in a Pharmaceutical Drug Product



Mathieu Boiret
HORIBA Scientific, Avenue de la Vauve, Passage Jobin Yvon, 91120 Palaiseau, France

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Resulting from the combination of Raman spectroscopy and optical microscopy, Raman hyperspectral imaging has proven to be an indispensable tool in the pharmaceutical field, especially to study the distribution of active(s) and excipients in a pharmaceutical drug product.

Introduction

In the pharmaceutical environment, and especially in the research and development field, the quality of the medicine is a critical step as it faces challenges with increased demand from the regulatory affairs to improve the quality of a pharmaceutical drug product. In order to ensure its proper effect on the patient health, a product has to be manufactured with exacting quality.

During pharmaceutical development or quality control, analysts must ensure the distribution of active(s) and excipients in the tablet. Indeed, the distribution of compounds is directly linked to the product stability (i.e. modification of crystalline form or degradation), active content (especially required for scored tablets) and drug release (agglomerates can modify the release profile). Raman images make possible the characterization of the pure compound in a pharmaceutical drug product and can provide its spatial distribution on the surface of a sample. It is non-destructive, and offers fast, versatile chemical identification within a small compact benchtop instrument. Excipients and actives can be analyzed within seconds, and extensive Raman spectral libraries allow easy chemical identification. More subtle changes in structure, such as polymorphism and crystallinity can also be investigated. Both can have strong influence on drug dissolution and efficacy, so understanding the true nature of an active is critical to the success of drug development and manufacture.

Conditions of Measurements

For the collection of the hyperspectral datacube, the XploRA equipped with a 532nm laser was used. The data were collected with the LabSpec 6 software and analyzed

by using all the powerful functions within the software.

The XploRA brings Raman chemical identification directly to your microscope. Combining microscopy and chemical analysis, the system retains the full functionality of your microscope, coupled with high performance Raman spectroscopy. Compact and rugged in design, the XploRA is easy to use and transport due to its minimal footprint, making it the ideal smart microscope for every R&D, QA/QC and forensic lab.

Results

In figure 1, three Raman maps have been acquired, moving from a large area low resolution whole tablet image, to a high resolution small area of interest to analyze individual grains/particles in detail. In the whole tablet map (a), which comprises 50,901 pixels over a 7 x 18 mm² area, the major constituents of **Aspirine**, **Paracetamol** and **Caffeine** are visible, in addition to the tablet coating (pink color). A higher resolution image (b) highlights a fourth component (**Cellulose**) widely spread across the tablet, but present only in small and discrete areas. The final image (c) was acquired with 2 μm step (90,601 data points), and allows the size and shape of individual cellulose grains to be observed.

A Chemometrics method, Classical Least Squares (CLS), available in LabSpec 6 software, was applied to a selected area to assess the percentage of each compound in the formulation. As presented in table 1, in the selected area, semi-quantitative analysis shows that Aspirine, Paracetamol, Caffeine and Cellulose represent respectively, 16.3%, 60.0%, 6.3% and 17.3% of this total area.

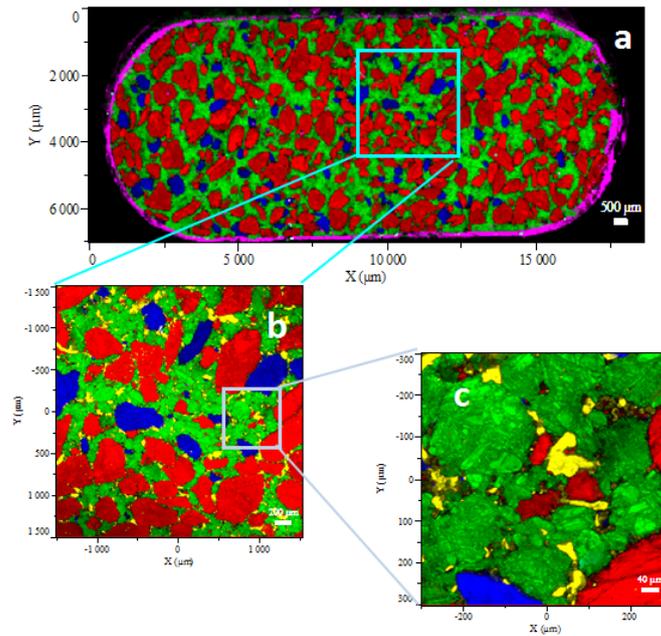
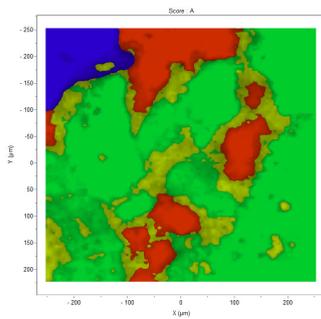


Figure 1: Color-coded Raman images of a pharmaceutical tablet highlighting the spatial distribution of the various components at different scales, to explore the tablet uniformity, as well as the grain size and boundaries



Compounds	Area (%)
Aspirine	16.3
Paracetamol	60.0
Caffeine	6.3
Cellulose	17.3

Table 1: Distribution of Aspirine, Paracetamol, Caffeine and Cellulose in percentage of the total area

Conclusion

Raman microscopy can now be considered as a powerful analytical tool in the pharmaceutical environment through the entire drug product life cycle, from drug discovery to post-marketed analysis. It provides information on compound identification and solid state characterization, but also information on spatial distribution of compounds, particle size analysis and homogeneity of the distribution.