Christos Kontoyannis[1,2]
Malvina Orkoula[1,2], Stefani Fertaki[1,2]
1) Department of Pharmacy, University of Patras, GR-26504 Rio Achaias, Greece
2) Institute of Chemical Engineering Sciences, Foundation of Research and Technology-Hellas (ICE-HT/FORTH), GR-26504 Achaias, Greece Platani

kontoyan@upatras.gr

Searching for micro-Raman LoD: The case of Tiotropium Br in Spiriva® and Braltus® formulations.

One of the advantages of micro-Raman spectroscopy is the point-by-point mapping resulting in higher sensitivity for the identification of low-content ingredients. According to International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH), the common approaches used for LoD determination are based on visual evaluation, signal-to-noise or on the standard deviation of the response and the slope [1]. In micro-Raman mapping spectroscopy though, numerous spectra are collected in order to possibly identify one spectrum of a component at low concentration and thus, ICH methods are not expected to be adequate.
Currently there is no established method for the determination of the LoD using micro-Raman mapping spectroscopy in solids (mRMLD). Also, there is no established methodology for the optimization of the scanning parameters taking into account factors such as the nature of the components, the particle size and the dispersion of the API in excipients (manufacturing process) that can influence the mRMLD. Several and different attempts for the LoD calculation of micro-Raman mapping were previously performed. In some studies, the LoD was extracted from the construction of calibration line from known calibrants using multivariate methods but an LoD range was calculated and not as an absolute value [2]. Others are more often based on the visual evaluation of the detected impurity at extremely low but known concentrations. The lowest recorded LoD between two polymorphs was found at 0.01%w/w [3] although the correlation between API particle size and lens or step was not checked. Such shortcomings were addressed in this work in an effort to establish a methodology/protocol for determining the mRMLD.
As case study the Spiriva® inhalation spray (Boehringer Ingelheim) was selected which contain only 0.4 w/w% of tiotropium bromide. This API exists in two forms, as anhydrous and as monohydrate. The X-Ray diffraction technique, which is usually used for polymorph discrimination, could not be applied succesfully due to the extremely low content of the API in the formulation. Tiotropium Bromide is present in the Spiriva® formulation in its monohydrate form. In order to establish the mRMLD the experimental parameters were optimized e.g. step size, scanning mode, objective lens, laser power and accumulations, by taking also into account the API particle size, area scanned, manufacturing process and Raman spectra and the sample was scanned using a long-time map. After the mapping, the value obtained from the Concentration of each of the API forms (monohydrate and anhydrous) in the test sample divided by the Number of spots (spectra) of the form detected, corresponded to the respective mRMLD. This was verified by appropriate sample dilutions and found to be inversely proportional to the number of scans. Micro-Raman mapping spectroscopy was capable to detect and discriminate between the two tiotropium bromide forms. The method was applied also on Braltus® formulation which contains anhydrous API and the manufacturing method includes spray dry instead of Spiriva's® direct mixing.

References

[1] ICH, Q 2 (R1) Validation of Analytical Procedures: Text and Methodology,
[2] E.M. Paiva et al. / Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy 228 (2020) 117798
[3] Mark J. Henson and Lin Zhang, Drug Characterization in Low Dosage Pharmaceutical Tablets Using Raman Microscopic Mapping, Applied Spectroscopy, Vol. 60, Issue 11, pp. 1247-1255 (2006)

Figures

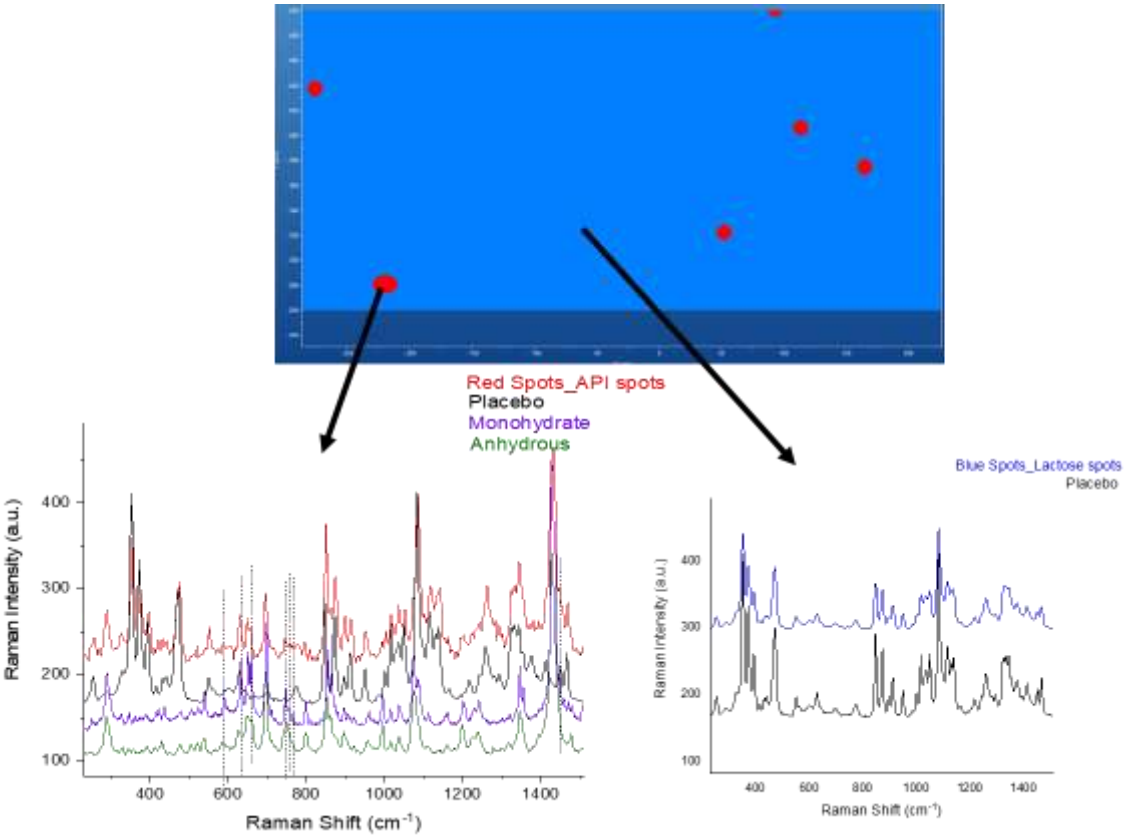

Figure 1: Typical Raman map of Spiriva® inhalation spray and the Raman spectra of the two present components.

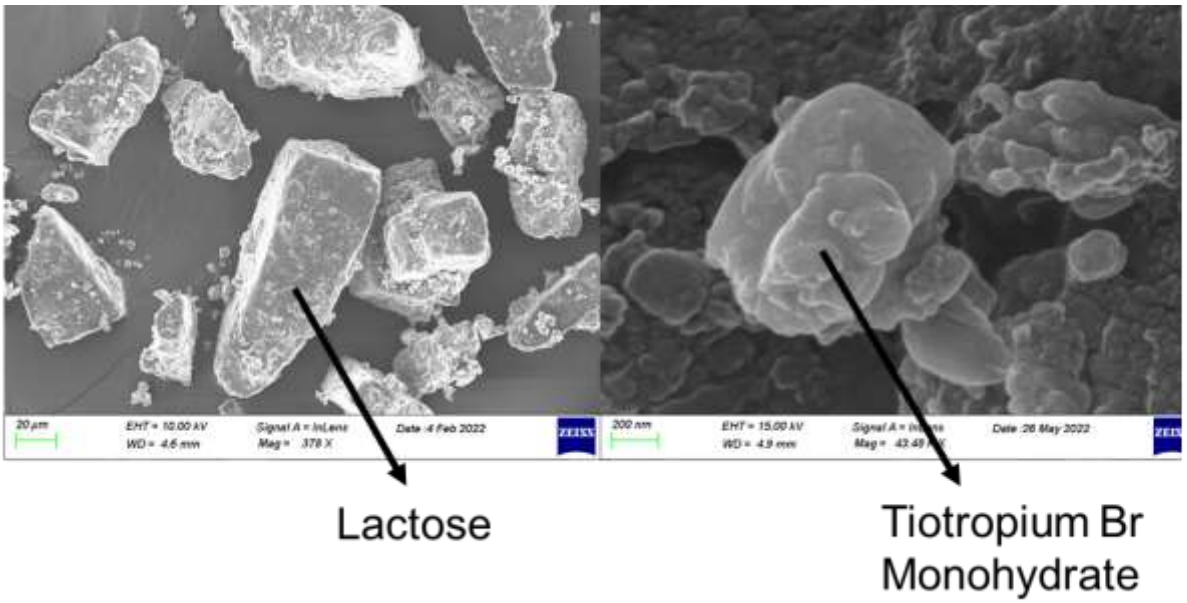

Figure 2: SEM images from EDX analysis of Spiriva® inhalation spray at 378 x magnification (only carriers are visible) and at 44k x magnification (focusing on a API particle on the lactose carrier).