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APPLICATION NOTE – JAGIELLONIAN CENTER OF INNOVATION

DISTRIBUTION OF THE ACTIVE SUBSTANCES IN THE TABLET ASSESSED WITH TOPOGRAPHIC RAMAN IMAGING

dr Emilia Staniszewska-Ślęzak*

**Laboratorium Obrazowania, Jagiellońskie Centrum Innowacji; ul. Bobrzyńskiego 14, 30-348 Kraków*

INTRODUCTION

Raman spectroscopy (RS) has been successfully applied in the pharmaceutical industry for past several years. RS is used for the rapid identification of the chemical compounds in the analysis of drug mixtures, including both – active substance and excipients. It allows to identify impurities, characterize preparations and provide information on the mixing processes of pharmaceutical ingredients. [1-3].

The aim of the conducted research was to show the application possibilities of the topographic Raman imaging technique. The subject of the study was a commercially available tablet containing three main active substances: paracetamol, propyphenazone and caffeine.

METHODOLOGY

All the Raman measurements, including collection of the API standard single spectra as well as Raman imaging of the tablet with topography surface correction, were carried out on the WITec Alpha 300RSA+ spectrometer combined with confocal microscope and equipped with TrueSurface® and EMCCD detector for ultra-fast and sensitive imaging. Raman spectra were collected using 532 nm excitation wavelength and the air objective 20x (Zeiss, NA=0.4). Spectral resolution was equal to 3 cm-1, and the spectra were recorded within 0 – 3600 cm-1 range. Raman imaging of the tablet was preceded by topography surface correction provided by TrueSurface® component with optimized measurement parameters ensuring high quality of the obtained results.

RESULTS AND DISCUSSION

In *Figure 1* there are presented Raman spectra for all three measured API standards: paracetamol, propyphenazone and caffeine. Based on them were chosen Raman marker bands used for API identification and distribution characterization in the imaged tablet. Their positions are as follow: 2935, 1655, 1329, 859 cm-1 for paracetamol; 3077, 1663, 1624, 1599, 998, 600 cm-1 for propyphenazone and 2962, 1703, 1332, 559 cm-1 for caffeine.

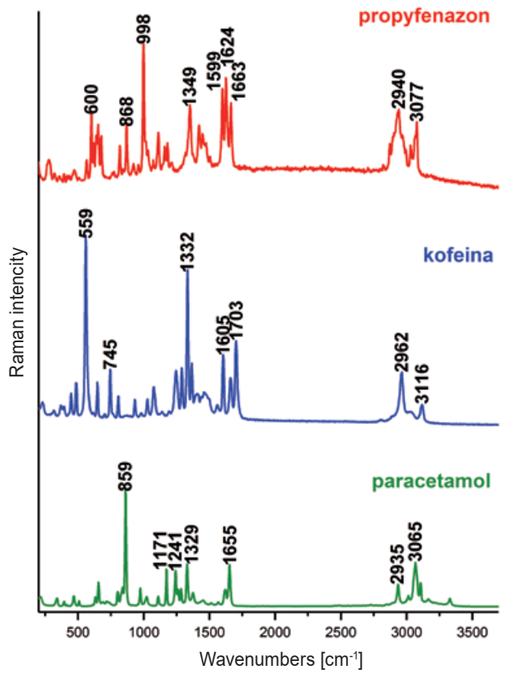


Figure 1. *Raman spectra for all three measured API standards: paracetamol, propyphenazone and caffeine acquired with use of 532 nm excitation wavelength.*

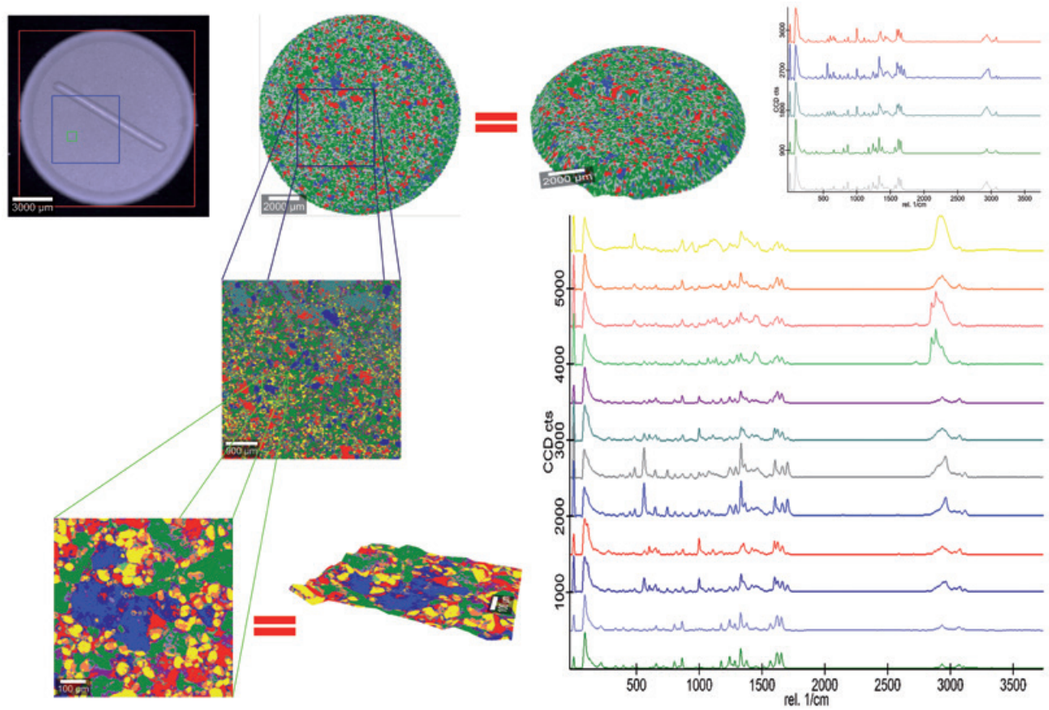


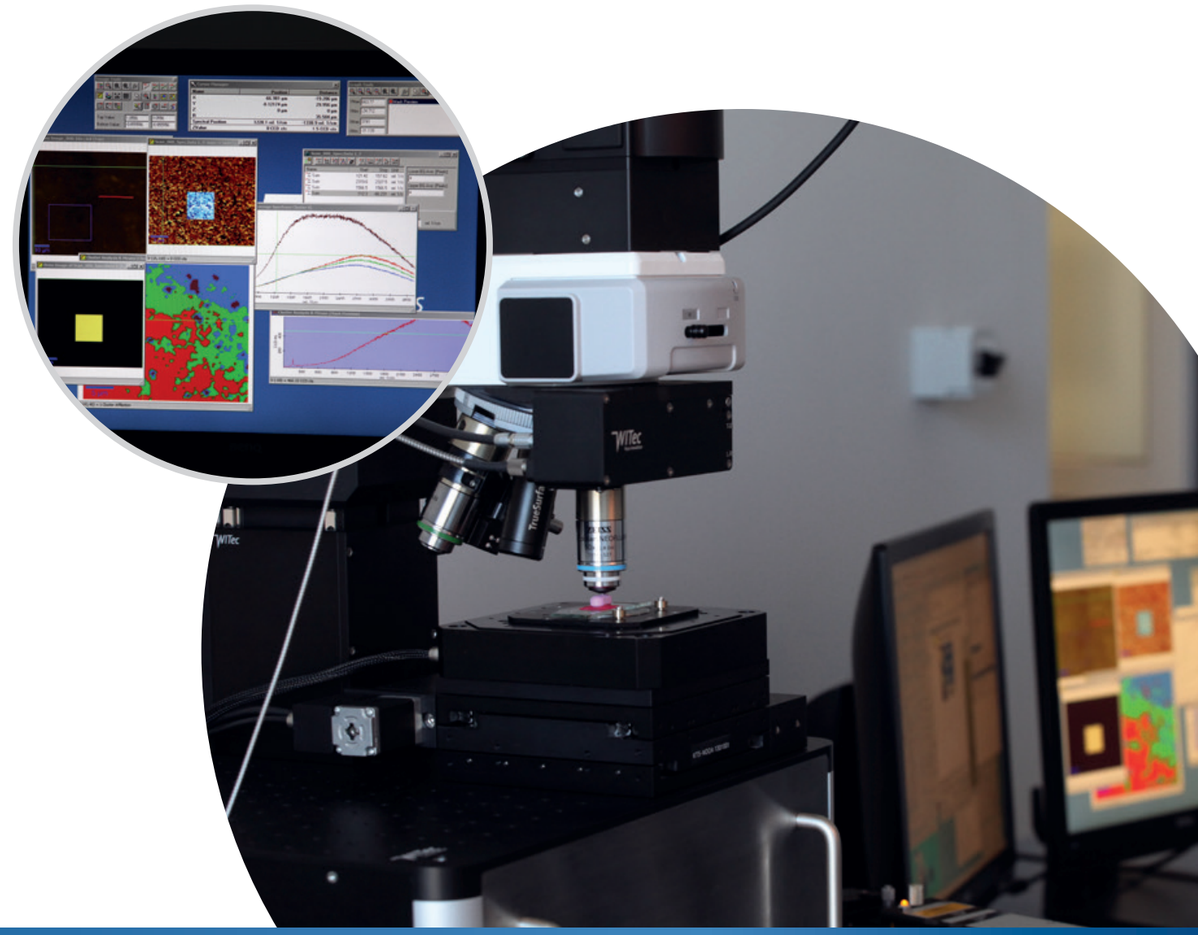
Figure 2. *Characterization of spatial distribution of the tablet ingredients, both, active substance and excipients, together with average Raman spectra extracted from each cluster obtained with use of k-mean cluster analysis. Each color corresponds to the color of the cluster.*

Firstly, the tablet was imaged with low spatial resolution to obtain the overall information about substance distribution. Subsequently, smaller fragments of the tablet were imaged with higher spatial resolution obtaining more detailed and precise information about the API distribution. Due to topography surface correction, intensity of the Raman signal was maintained throughout whole measurement. The acquired images allow also to present distribution as 3D image. The set of collected Raman images is presented in *Figure 2.*

K-means cluster analysis revealed 12 clusters within the studied tablet. Beside the three main components identified as active substances: paracetamol (green cluster), propyphenazone (red cluster) and caffeine (blue cluster), also tablet excipients such as fatty acids and starch were identified. It should be emphasized, that none of these excipients occurred alone, but co-existed with API. Fatty acids have been identified in clusters color-coded: aquamarine (a mixture of fatty acids and paracetamol) and peach (a mixture of starch, fatty acids and paracetamol), whereas starch occurred in clusters color-coded: yellow (mainly starch with a small addition of paracetamol), orange (a mixture of paracetamol and starch), gray (a mixture of caffeine and starch). Due to applied chemometrics, the coexistence of API in various ratios was noted, which was included in clusters color-coded: violet, turquoise, navy blue and light gray assigned to mixtures of: paracetamol and propyphenazone, propyphenazone and caffeine, caffeine and propyphenazone, and paracetamol and caffeine, respectively.

SUMMARY

Performed Raman imaging allowed to identify all three active substances and excipients present in the measured tablet, regardless the size of the imaged area. By reducing the size of the imaged area it was possible to greatly improve spatial resolution. Application of chemometrics, i.e., k-means cluster analysis, allowed for differentiation and characterization of spatial distribution of active substances and excipients found in the tablet. In some of the areas, their co-existence was observed. Topography surface correction enabled maintenance of the Raman signal intensity regardless the roughness of the tablet surface, which could otherwise cause interferences during measurement leading to drop in Raman signal quality and eventually lead to misleading observations.



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CONTACT

dr Emilia Staniszewska-Ślęzak
Kierownik Laboratorium Obrazowania

M: +48 515 474 671
E: emilia.staniszewska@jci.pl

Jagiellońskie Centrum Innowacji Sp. z o.o.
ul. Bobrzyńskiego 14, 30-348 Kraków

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