Raman Imaging for Characterization of Novel Multi-Layer Solid Dosage Forms

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ABSTRACT

In the present study, Raman image analysis for a sectioned 1 mm diameter bead dosage form was utilized to expose the multi-layer structure of the bead, to find distribution profiles of API and excipients, and to determine size and shape of microparticles in the core unit of the bead. The full-area visual and Raman image inspection was performed to select areas of interest to be then imaged at spatial resolutions as high as 1 micron. Analysis of individual spectra from different locations was conducted to validate stability of the API throughout the bead. Raman chemical images obtained with the use of Thermo Scientific DXR Raman Microscope provided high chemical selectivity and spatial resolution to be particularly suited for the analysis of novel multi-layer dosage forms.

Keywords: Raman spectroscopy, Raman imaging, pharmaceuticals, tablet.

1 INTRODUCTION

Multi-layer and core tablets are getting increasing attention in pharmaceutical industry. These novel delivery systems are important in helping pharmaceutical companies to improve efficacy due to the tailored release profiles and separation of active ingredients (APIs) that may be obtained as well as to find solutions that can extent the companies' product patents [1].

As an insufficient control in manufacturing the multi-layer dosages can result in significant variability in the product properties and performance, the development and application of techniques for physicochemical characterization of the final product becomes of a major importance.

From the array of molecular spectroscopy techniques used for the characterization of heterogeneous solid-dose products [2], Raman spectrochemical imaging has been shown to be an effective method to determine API and excipients distribution, particle/domain size and shape, aggregation and phase separation, preferred association of components, possible delamination and cross-contamination between constituents [3].

In Raman spectrochemical imaging, the spectra are acquired in pre-defined spatial positions (area map) and processed using specialized software to provide a two-dimensional representation (image) of the chemical composition of the sample under study. This image can be constructed from spectral properties that reflect the chemical composition of the sample such as spectral correlations, intensities or areas of Raman peaks specific for the component of interest, ratios of the intensities or areas, and other univariate or multivariate measurements [4].

2 EXPERIMENT

A bead with diameter of ~1 mm from a multiparticulate dosage form [5] has been used for the experiment. The bead was cleaved in halves with flat surfaces and one half of the bead was aligned to be parallel to the horizontal axis of the sample stage of Thermo Scientific DXR Raman microscope used to map the cleaved surface throughout the bead.

Raman spectra were obtained by exciting the bead with a laser line at 780 nm to minimize fluorescence that usually originates from pharmaceutical excipients under visible excitations. The map comprising the whole circular cross-section of the bead has been collected through 20X objective from the grid of 2500 points at 20 micron (μm) equidistant spacing along both *x* and *y* directions. The full-area visual and Raman image inspection and analysis have been performed to select areas of interest to be then imaged at higher spatial resolutions. The maps containing specific areas of the bead have been obtained through 50X or 100X objectives with step sizes down to 1 μm. The spectra in each map were recorded in confocal mode with 50 μm pinhole aperture in the range of 3400-50 cm^{-1} with 4 cm^{-1} spectral resolution. The total map collection times have varied from half-hour to several hours depending on the mapped area size and the number of point inside each area.

The Raman maps were collected and the images shown here were constructed using OMNIC Atlμs software.

3 RESULTS

Raman image analysis of the whole cross-section of the bead has allowed the layered distribution of API, ethyl cellulose, talc, and the core unit composed of mixture of sugar and starch to be clearly identified and thickness of the layers and the core unit size to be readily determined. Raman images showing the distribution of the components in the bead are illustrated in Fig.1. The Raman images were constructed as correlations with the reference spectra of corresponding excipients that are known to be in the composition of the dosage form. The Raman images for API were constructed as self-correlations due to a very

strong Raman response from the API. It is clearly seen that API constitutes a main layer and is mixed with talc in the adjacent intermediate layer. Comparing Raman spectra from the layers, it was found that API presents in a correct polymorphic form and there was no change in the form in its mixture with talc in the intermediate layer.

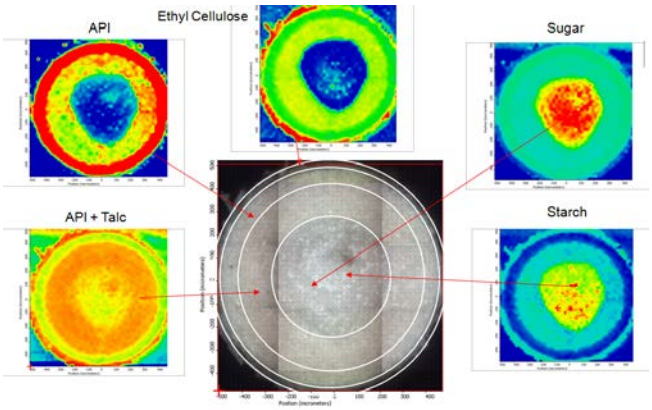

Fig.1. Visual (center) and Raman images of the full cross-section of the bead constructed as spectral correlations with reference spectra of the corresponding compounds – red color indicates the areas of the highest correlation and, thus, concentration of the compounds.

Fig.2 shows distribution of the API and the excipients in a selected area of the bead. The Raman images evidence for the sharp boundary between the inert sugar-starch core unit and the intermediate API-talc layer coated over the inert core unit. Agglomeration of talc in domains some of them reach up over 20 μm in dimensions is seen in the intermediate API layer and in the main one in a smaller extent. No cross-contamination between the inert core and the API-containing layer was established.

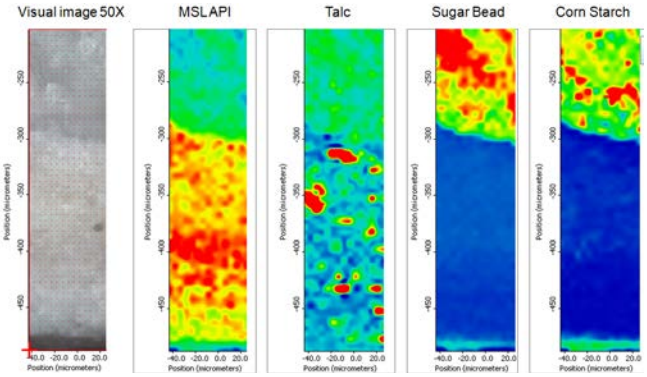

Fig.2. Spatial distributions of API and excipients in 70 x 285 μm area (870 spectra, 5 μm spacing).

Fig.3 illustrates the ability to image excipient particles with 1 μm spatial resolution in confocal Raman measurements. Starch microparticles in the mixture with sugar in the bead core were shown to have a spherical shape and diameters ranging from 5 to 10 μm.

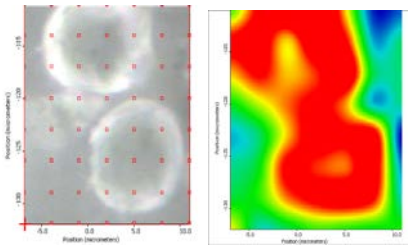

Fig. 3. Spherical starch particles mapped with 1 μm spatial resolution.

One-dimensional lines extracted from area maps allow direct analysis of concentration profiles in the multi-layer bead.

4 CONCLUSIONS

Raman spectrochemical imaging is a powerful technique for characterization of multi-layer solid dosage forms. This technique provides manufacturing process in the pharmaceutical industry with an analytical tool for the end-product content uniformity, stability and drug-excipients compatibility testing.

DXR Raman Microscope allows any areas of sectioned tablets to be mapped with an optimal up to sub-micron spatial resolution. Raman images from the mapped areas can be obtained rapidly with no compromise in spectral resolution using OMNIC Atlμs software for quick and easy generation of the images using either univariate or multivariate (chemometrics) models.

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