

Confocal Raman Microscopy - Imaging in the Pharmaceutical Industry

In the pharmaceutical industry, it is important to know as much as possible about the structure and distribution of the active components within surface coatings of medical devices or a variety of other forms. Confocal Raman Microscopy provides the ability to non-invasively map chemical properties of such samples at the highest resolution and to acquire depth profiles.

Medical Devices - Tubes

In this experiment, a coating (PhotoLink™) on a polyurethane catheter was

investigated. Between the PhotoLink reagents and the device surface, a strong carbon-carbon bond was formed, producing a stable and high-quality coating.

Using the Spectral Imaging Mode of the CRM 200, a spectrum at each pixel was acquired by performing a scan in the z-direction.

Fig. 1 shows the cross-sectional Raman image of the PhotoLink coating on a polyurethane catheter. The distribution and structural composition of the coating is clearly illustrated.

The Raman spectrum (fig. 2) is a fingerprint of the coating chemistry and can be used to generate color coded images of the coating's depth profile.

Raman imaging not only reveals the thickness of the coating and its uniformity, but can also identify and image drug polymorphs. Even though the Raman spectra of amorphous and crystalline drugs differ only slightly (fig. 4), the sensitivity of CRM 200 allows drug polymorphs in coatings to be clearly distinguished (fig. 5).



Fig. 1: Image of the PhotoLink coating on a polyurethane substrate.

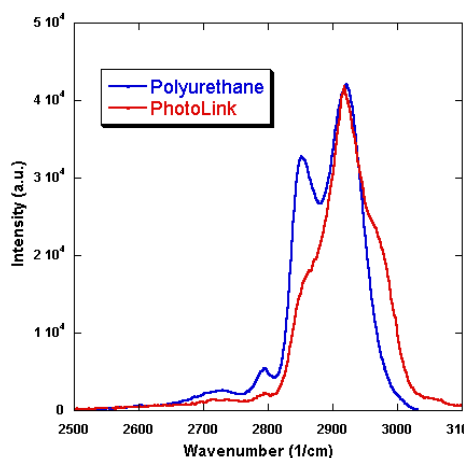


Fig. 2: Raman spectra of the PhotoLink coating and the polyurethane catheter.

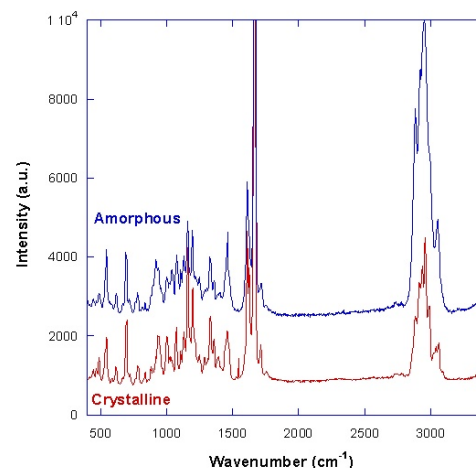


Fig. 4: Raman spectra of amorphous and crystalline drug components in a coating.

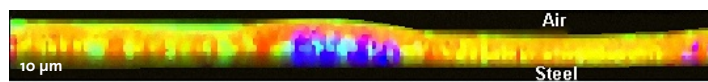


Fig. 5: Cross-section of a drug-delivery coating plus polymer on a stent. Polymer (red), amorphous drug (green), crystalline drug (blue), polymer + amorphous drug (yellow).

Solid pharmaceutical forms

As an example of the surface chemistry mapping capabilities of the CRM 200, a tablet containing acetylsalicylic acid (ASA) was examined within a scan range of $180 \times 180 \mu\text{m}$ and 120×120 pixels (= 14400 spectra). Integration time was only 50 ms/spectrum. In order to optimize the signal to noise ratio, fit procedures can be performed by the integrated software tools. From a small region of interest, a basis spectrum is generated by averaging all spectra within this area. These basis spectra can be fitted to the measured spectra, resulting in an optimized image. The three images obtained by the fit procedure were combined into one colored image

(fig. 6). Fig. 7 shows a zoom-in of the marked area in fig. 6 and in fig. 8 a depth scan with $180 \mu\text{m} \times 20 \mu\text{m}$ is shown.

The green and red areas show the pure ASA (green and red spectra in fig. 9) in different configurations, whereas the blue regions (corresponding to the blue spectrum in fig. 9) are the excipients.

Ointment

With the CRM 200, it is also possible to show the distribution of multiple components in an ointment. For this experiment, a commercial ointment was deposited between two cover slips and imaged with an oil

immersion objective (N.A. = 1.25). The scan range was $20 \mu\text{m} \times 20 \mu\text{m}$ and 120×120 pixels (= 14400 spectra) with an integration time of only 100 ms per spectrum. With special software tools, the spectrum of the agent Dex-Panthenol in this case, could be extracted from the measured spectra. In order to verify the generated spectrum, the pure substance was also analyzed (fig. 11). The image in fig. 10 was then created by the same fit procedure described above. Fig. 12 shows a depth scan and fig. 13 shows the corresponding spectra in which the blue spectrum belongs to the Dexpanthenol (dissolved in water) and the red and green spectra correspond to the ointment bases.

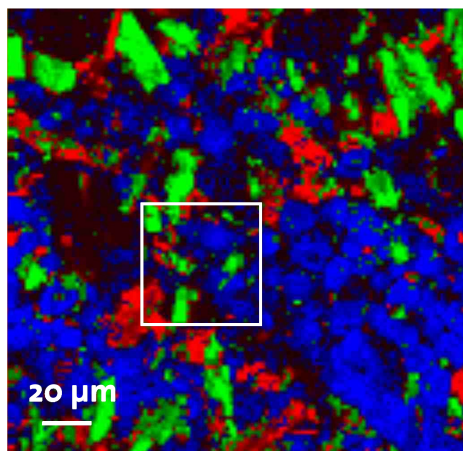


Fig. 6: Distribution of ASA and excipients.

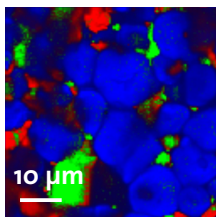


Fig. 7: Distribution of ASA and excipients (zoom-in, marked region in fig. 6).

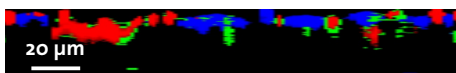


Fig. 8: Distribution of ASA and excipients, depth scan.

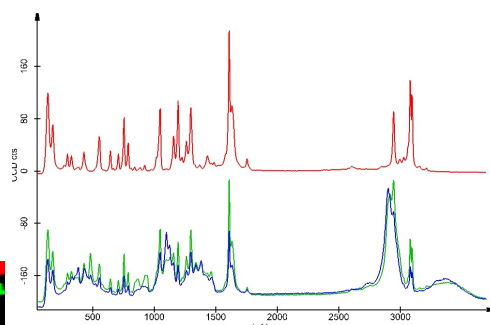


Fig. 9: Corresponding spectra of ASA in different configurations (green and red) and excipients (blue).

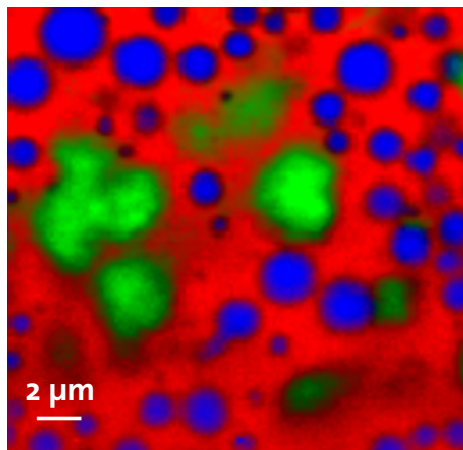


Fig. 10: Distribution of Dexpanthenol (dissolved in water) and ointment bases.

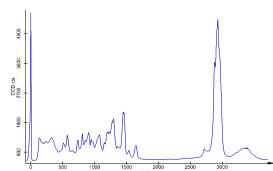


Fig. 11: Single spectrum of Dexpanthenol

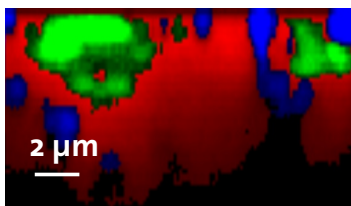


Fig. 12: Distribution of Dexpanthenol, depth scan.

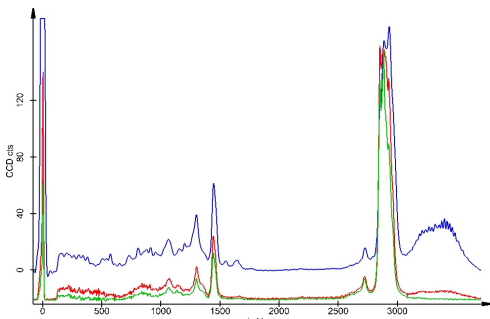


Fig. 13: Corresponding spectra of Dexpanthenol (blue) and ointment bases (green and red).