

Confocal Raman analysis of a transdermal nicotine patch by a DXR2 Raman Microscope

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Application benefit

Confocal Raman microscopy provides a facile means to analyze multilayer polymers and to identify the active pharmaceutical ingredient (API) in a nondestructive manner with minimal sample preparation.

Keywords

Confocal Raman microscopy, Transdermal patch, Chemical mapping, Multilayer polymer



Figure 1: DXR2 Raman microscope

Introduction

Transdermal patches are medication delivery systems that adhere to the skin and deliver drugs through a controlled release into the skin and then into the bloodstream. Nicotine transdermal patches are a form of nicotine replacement therapy used to aid in smoking cessation.

Transdermal patches have multiple layers: the release liner, the adhesive, the membrane, and the backing. The release liner protects the adhesive and drug formulation and is removed prior to application. The adhesive adheres the patch to the skin. The membrane layer (or layers) contains the drug and controls the rate of diffusion of the drug out of the patch and into the skin. The backing is the outermost layer of the patch and protects the formulation while the patch is worn.

It is important to understand the composition of a transdermal patch to perform quality control and product improvement, and to monitor the drug release mechanism. Traditional methods of analysis are typically destructive, either requiring dissolving the sample for extraction (e.g., GC-MS, LC-MS) or physically cross-sectioning the patch (e.g., SEM, TEM). Using confocal Raman analysis by the Thermo Scientific™ DXR™2 Raman Microscope, the layers of a commercially available transdermal nicotine patch were examined without sample destruction.

Experimental

A transdermal nicotine patch sample was mounted onto a gold-coated microscope slide with the backing layer facing the microscope objective, and the release liner at the bottom. Raman confocal line depth profiling and area depth profiling were performed with a DXR2 Raman microscope (Figure 1) using 532 nm laser, 5 mW laser power at the sample, 50X objective, 25 μm confocal pinhole aperture, and with auto exposure (S/N = 200). For the line depth profiling (Z-profiling), a depth of 220 μm was probed by using a 5 μm step size (containing 45 points or spectra). For the area depth profiling, a vertical X-Z area of 120 μm (X) by 245 μm (Z) was probed by using a 5 μm step size along the Z-axis and 20 μm along the X-axis. The area is composed of 350 points or spectra.

To correlate an optical image with the Raman profile, a small cross sectional piece of the nicotine patch was mounted vertically on the glass slide.

The Thermo Scientific™ OMNIC™ for Dispersive Raman Software Suite, which includes Thermo Scientific™ OMNIC™ Atµs™ Software, was used for data collection, processing, and analysis, including identification of the layer composition and estimation of the layer thickness. The multi-component spectral analysis was performed using Thermo Scientific OMNIC Spectra Software.

Results and discussion

A Raman line depth profile map obtained using the OMNIC software suite is shown in Figure 2a. In the figure, the depth profile is displayed in a 2-D contour map and reveals the changes in the Raman peaks (vertical lines) as the focal point probes through the layers. The rainbow color scheme of the contour map shows the intensity of the Raman peaks as color, with red indicating the highest intensity and blue the lowest intensity. A total of six layers were identified with thicknesses ranging from ~15 µm to ~75 µm. The thickness of each layer was estimated by the full width

at half maximum (FWHM) value method described in the Thermo Scientific Application Note 51718¹. Figure 2b shows the optical image of the physically cross-sectioned sample. The optical image provides a visual representation of the layer thickness based on contrast and although it is comparable to the chemical image, some of the layers are not easily identifiable.

Figure 3 shows the representative Raman spectra for each layer in the Raman line depth profile. The chemical composition of each layer was initially identified by performing a library search against the Thermo Scientific High-Resolution Raman Polymer Library using OMNIC software.

Layer 1, the backing is poly(ethylene terephthalate) or PET. Layers 2 and 4 are composed of microporous polyethylene (PE) that acts as a controlled release agent for nicotine, which is located at the ethylene/vinyl acetate copolymer (EVA) reservoir layer (layer 3). Layer 5 is a polyisobutylene (PIB) adhesive and PET. Layer 6, the release liner is also composed of PET.

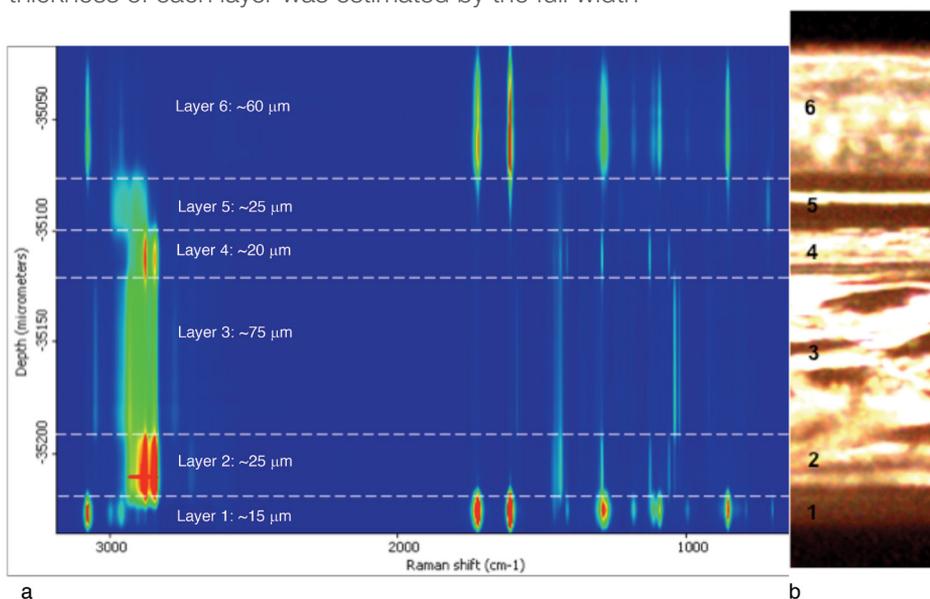
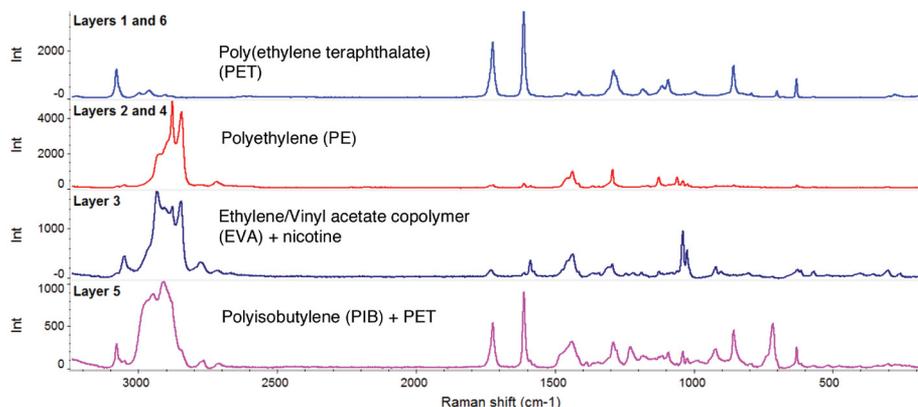


Figure 2: a) Raman line depth map (Z-map) for the transdermal nicotine patch. The dashed white lines indicate the approximate depth of each of the six layers. b) An optical image of the cross section.

Figure 3: Representative Raman spectra for each layer of the patch.



The presence of nicotine in the EVA reservoir layer (layer 3) was identified by the OMNIC Spectra software using the Multi-Component Search option, as shown in Figure 4. The patented Multi-Component Search allows one to identify constituents in mixture samples without the tedious manipulations required by the traditional search and subtract processes. Not only did the search identify S-(-)-nicotine as the second component (green in Figure 4), in addition to the EVA (orange), it also provided the composite value (%) of the two components. The composite value is a scaling factor indicating the amount of each found reference represented in the composite spectrum. It should be noted, however, that the composite values cannot be taken as a quantitative percentage of the materials, which requires measurements by a primary quantitative analytical technique.

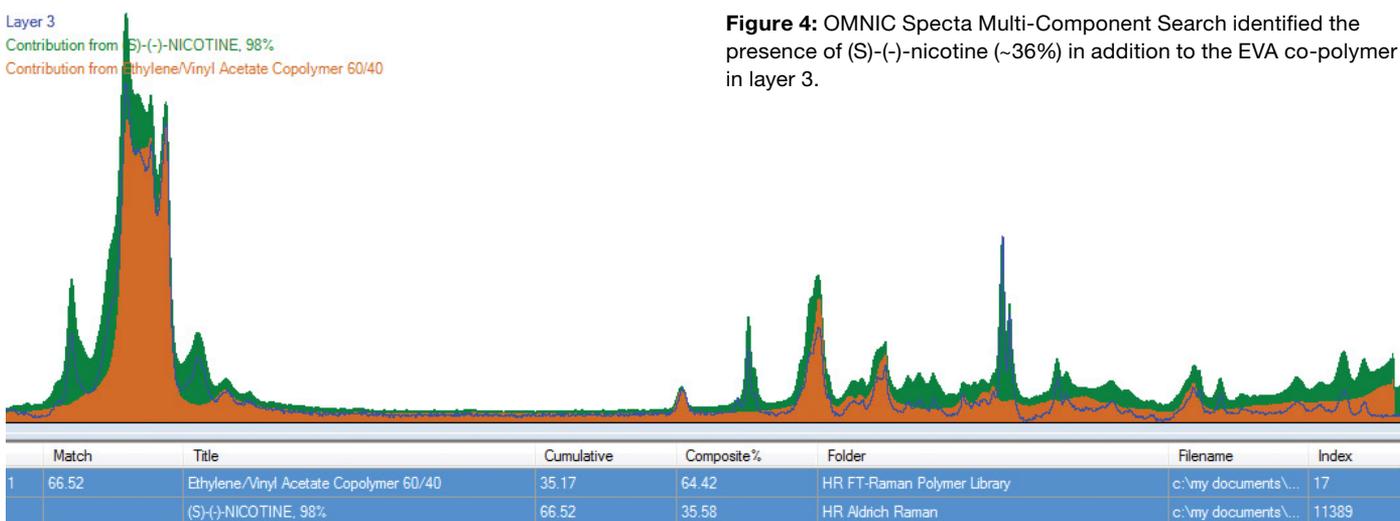


Figure 5 shows correlation profile images obtained from the Raman confocal area depth (X-Z) profiling of the same nicotine patch sample. Each of the images was obtained by using the correlation between the map spectra and the reference Raman spectrum of each layer. The red color in the images indicates the highest correlation to a specific reference spectrum, whereas the blue indicates no correlation. For example, the EVA+nicotine correlation image (Figure 5, right) shows a single red colored layer indicating that this layer has the highest correlation to the EVA+nicotine reference spectrum, thus showing that this is the layer where these two components are located. The presence of 6 layers in these images is consistent with results of the confocal line depth profile analysis (Figure 2). In addition, the X-Z correlation images here reveal relatively uniform thickness of the layers.

Figure 4: OMNIC Spectra Multi-Component Search identified the presence of (S)-(-)-nicotine (~36%) in addition to the EVA co-polymer in layer 3.

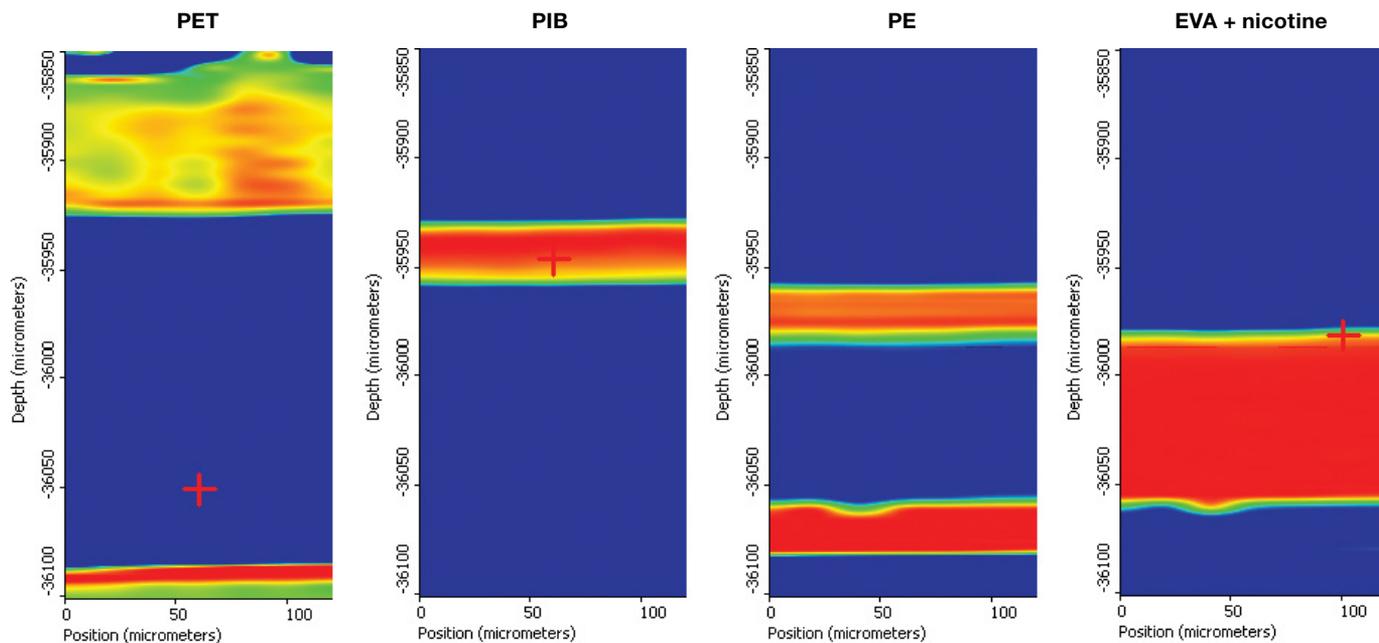


Figure 5: X-Z correlation profile images generated by the reference Raman spectrum of each layer.

Conclusion

Existing techniques for analyzing a multilayer polymer like a transdermal nicotine patch are labor intensive, time-consuming, and would require destruction of the sample. Using confocal Raman analysis, the analysis was quick, and the sample integrity was preserved. The chemical composition of each layer was determined using OMNIC for Dispersive Raman and OMNIC Spectra software suites. OMNIC Spectra Multi-Component Library Search identified the constituents in layer 3, a mixture of nicotine and an EVA co-polymer, which is easier than tedious manipulations required by traditional search and subtract processing.

References

1. Guillory P., Deschaines T., Henson P. *Confocal Raman microscopy analysis of multilayer polymer films*, Thermo Scientific Application Note 51718, 2008.

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