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Using Raman Mapping to Detect and Identify Challenging Degradation Products and Complex Drug-Drug Interactions in a Tablet

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PURPOSE

Raman mapping is a powerful technique for the analysis of pharmaceutical tablets. Thousands of spectra can be collected across the surface of a microtomed tablet, and these spectra can be analyzed to determine how the various components are spatially distributed. In addition, mapping data can also be used to detect and identify very low amounts of a component that would not be detectable if a bulk Raman technique was used. In this current study, we will present the results collected from area maps on two different regions of an expired tablet, where peak height ratio profiles and spectral subtractions were used to locate and identify degradation products.

METHOD(S)

An extra-strength Excedrin® tablet (expired July 2009) was prepared for analysis by shaving thin layers off the top until the coating was removed and approximately one fifth of the tablet thickness was removed. Raman mapping was conducted on a HORIBA Scientific XploRA series confocal Raman microscope on an Olympus series BX51TRF optical platform. Area maps consisting of 2601 spectra over a grid of 102 microns by 102 microns (step size 2 microns) were collected near the edge of the tablet and within the interior of the tablet. Reference spectra were obtained of the individual ingredients listed on the label. The spectra were examined for specificity and spectral peaks were identified that could be used to create the mapping profiles. A peak height ratio profile was most often used. Once the profiles were created for each ingredient, spectra were extracted from the map and compared to the reference spectra to confirm their identity.

Peaks were identified in the map collected at the tablet edge that did not belong to any of the known components. Profiles created for this unknown indicated that it was located between two of the active ingredients. Additionally, it was more prevalent towards the edge of the tablet. The unknown was identified, and a hypothesis was formed to explain its appearance. The hypothesis was then applied to a third active ingredient in the tablet and its degradation product was also found. Spectral subtractions were essential for confirming the presence of this last degradation product.

RESULT(S)

Using peaks specific for each (Fig 1), profiles were created for acetylsalicylic acid, acetaminophen, caffeine, HPMC, and microcrystalline cellulose (Fig 2). Locating and identifying the various excipients and active ingredients were accomplished. Of more interest, however, was the appearance of spectral peaks that did not correspond to any of the known ingredients.

Acetylsalicylic acid (an active ingredient) can decompose to form salicylic acid upon exposure to humidity. In addition, caffeine (an active ingredient) can react with salicylic acid to form caffeine salicylate. Caffeine salicylate was analyzed by Raman microscopy and confirmed to be present in the tablet map. Fig 3 shows a spectrum from the map (red), compared to reference spectra of acetylsalicylic acid, caffeine, and caffeine salicylate.

A profile was created for caffeine salicylate and found to be very similar to the profile for caffeine, suggesting that the compounds are intimately mixed in the tablet (Fig 4). To better spatially separate the caffeine from the caffeine salicylate in the mapping images, profiles were created comparing the peak height ratio of each one versus the other. This approach is very powerful at separating closely related compounds or detecting a compound present at a very low level. The resulting profiles indicated that the caffeine salicylate was more present in-between regions of caffeine and acetylsalicylic acid (Fig 5). Given the age of the tablet, water may have migrated through the coating, causing the decomposition of acetylsalicylic acid to salicylic acid, which then reacted with caffeine to form caffeine salicylate.

If this hypothesis is true, then the third active ingredient (acetaminophen) should degrade upon exposure to moisture to form 4-aminophenol. The mapping data were examined to determine if 4-aminophenol could be detected. Specificity was poor for this compound, as the strongest peaks were very similar to peaks in the acetaminophen spectrum. A small shift separated a relatively strong peak at 1170 cm^{-1} for 4-aminophenol to one at a slightly lower wavenumber for acetaminophen. A mapping profile for 4-aminophenol was created to interrogate this slight difference and revealed small regions where 4-aminophenol was more likely to be present (Fig 6). A spectrum for acetaminophen was extracted from the map and subtracted from a 4-aminophenol spectrum also from the map, finally confirming the identity of the suspected degradation product (Fig 7).

Fig 1. Reference spectra

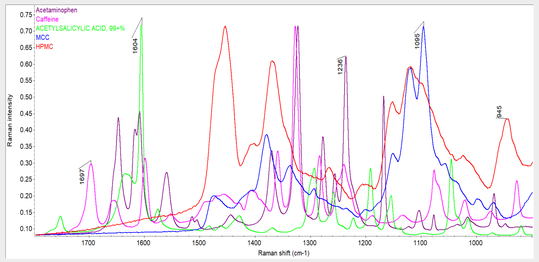


Fig 2. Profiles for (Top, L to R) acetylsalicylic acid, acetaminophen, caffeine; (Bottom, L to R) HPMC, MCC. (Note: red indicates high correlation; blue indicates low)

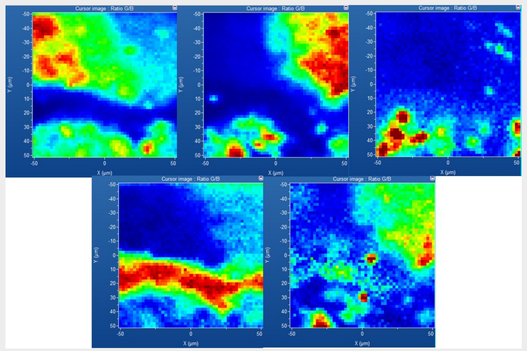


Fig 3. Identification of caffeine salicylate in a spectrum from the tablet map, compared to reference spectra

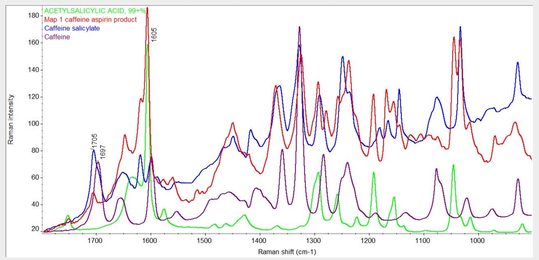


Fig 4. Initial profiles for caffeine (left) and caffeine salicylate (right)

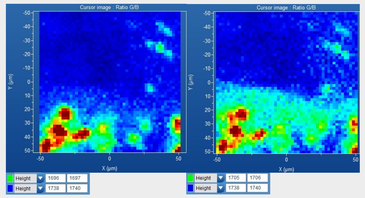


Fig 5. Profiles for acetylsalicylic acid (left), caffeine salicylate (middle) and caffeine (right)

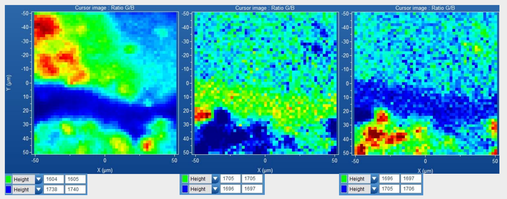


Fig 6. Profiles for acetaminophen (left) and 4-aminophenol (right)

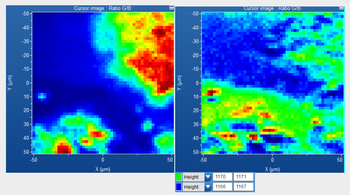
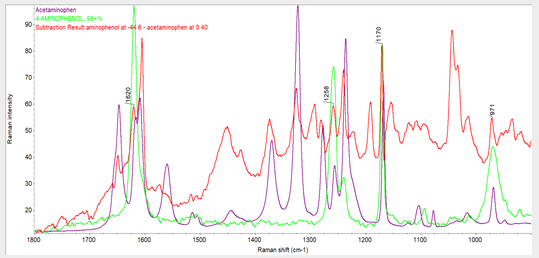


Fig 7. Identification of 4-aminophenol in a spectrum from the tablet map, compared to reference spectra



CONCLUSIONS

Although the use of Raman mapping to determine the spatial location of various ingredients in a tablet may be straight-forward, identifying unknown components and determining a likely cause for the appearance requires a more complex approach. Specific profile strategies, knowledge of possible chemical reactions that could be present, and spectral subtractions are often necessary to solve such problems. These tools were successfully used to interpret the Raman mapping data of an expired Excedrin tablet.

Evidence of degradation of both acetaminophen and acetylsalicylic acid was found. In addition, caffeine salicylate, a reaction product from a degradation product with caffeine was also found.

The location of the degradation products within the mapping area also indicates where moisture likely infiltrated the tablet. Viewing the mapping profiles, the caffeine salicylate degradation product is not only located between caffeine and acetylsalicylic acid but is also concentrated on the left edge of the mapping area (see Fig 5, middle profile image). The other degradation product, 4-aminophenol, is also concentrated in this same area. This side of the mapping image was located nearer to the edge of the tablet, which supports the hypothesis that moisture might have migrated through the coating.