Characterizing Multi-Layer Pharmaceutical Tablets

using the Agilent Laser Direct Infrared (LDIR) Chemical Imaging System

Benefits of the 8700 LDIR for investigating multi-layer tablets

- **Easy identification and measurement of constituent distribution in a tablet:** The user simply chooses the area of interest and selects the appropriate image pixel size. Based on the target component spectra, the Agilent Clarity software selects the diagnostic wavelengths that yield maximum chemical contrast. The results are directly displayed without any additional processing or data manipulation.
- **Excellent spatial resolution and field of view:** An image of a multilayer tablet can be acquired for a range of pixel sizes without switching optics, eliminating the need for instrument adjustment. Tablet constituent information can be acquired both for the bulk tablet and in finer detail at the interfaces of the layers without changing instrument optics. In ATR mode, a pixel size as small as 0.1 micron can be selected.
- **Fast comprehensive analysis:** The 8700 LDIR is equally sensitive to both excipients and active pharmaceutical ingredients, yielding complete answers much faster than Raman micro-imaging.

Chemical Imaging of Multi-layer Tablets

Multi-layer tablets are used to deliver many drug compounds since they allow:

- Release of one or more different active pharmaceutical ingredients (APIs) at different times
- Separation of ingredients that are incompatible if formulated together
- Combination of an immediate release layer and a sustained release layer so that an effective concentration of the drug is maintained over an extended period of time.

Formulating multi-layer tablets often gives rise to problems such as layer separation, cross contamination between layers, pressure-related degradation of active ingredients and the potential for increased impurities with the increased complexity of the formulation.

The Agilent 8700 LDIR Chemical Imaging System provides an effective means to study inter- and intra-layer interactions in multi-layer dosage forms. It reveals the distribution of the constituents of a tablet, including whether the rate-controlling polymers/compounds are correctly distributed in each layer. Because of the speed of analysis and spatial resolution provided by the 8700 LDIR, a detailed examination of the interfaces between layers is possible for both single and multiple samples.

The high-resolution images obtained using the 8700 LDIR provide valuable information about the composition of active ingredients and excipients in these types of tablets. This is useful in dosage formulation studies aimed at understand the relationship between composition and dissolution, as well as for quality control purposes to ensure that tablet manufacture is consistent.

Multi-Compound Identification

A mid-IR spectrum of a tablet constituent can be easily acquired in reflection or Attenuated Total Reflectance (ATR) modes by simply selecting a point of interest. The resulting spectrum can then be matched against library spectra for identification.

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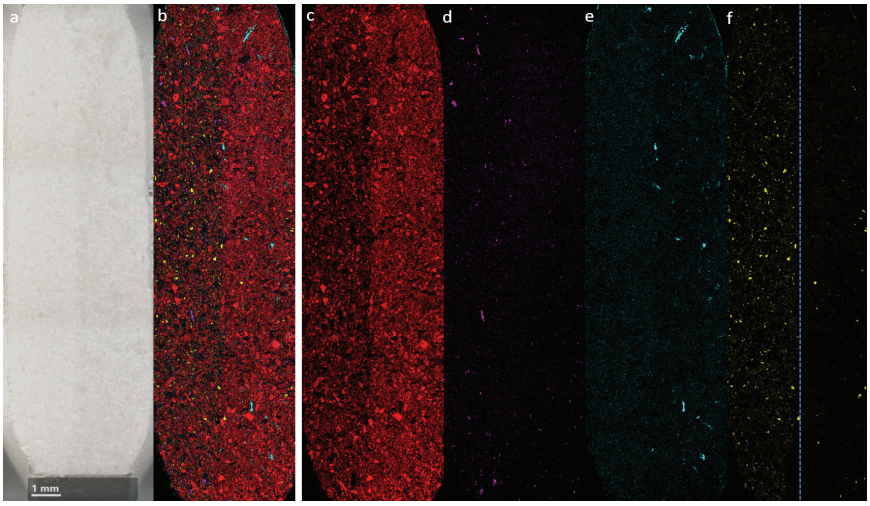

Figure 1. (a) Side view of the bilayer tablet, with the unprinted side on the left and the printed side on the right. (b) A composite image of images c-f, showing all the constituents. (c-f) Show the individual chemical maps of acetaminophen (c), cellulose (d), hydroxyethyl cellulose (e), and starch (f). The vertical blue dashed line in (f) to highlight the separation of layers. The scale bar in 1 mm.

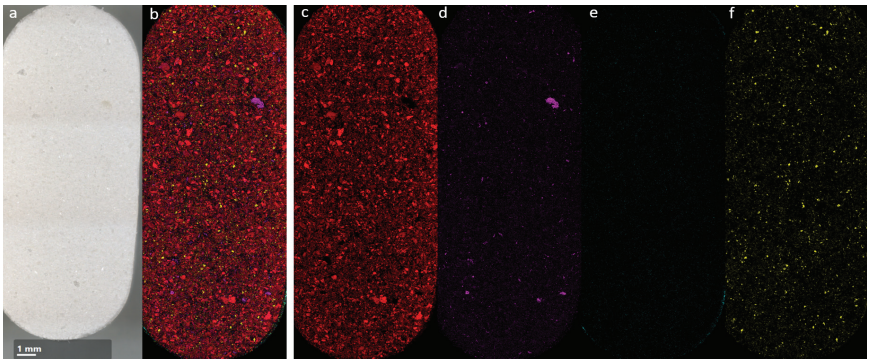

Figure 2. (a) Visible image of microtomed unprinted side of tablet facing up. (b) The composite image with all the constituents of the unprinted side of the tablet facing up. (c-f) The individual chemical map of acetaminophen (c), cellulose (d), hydroxyethyl cellulose (e), and starch (f). The scale bar is 1 mm long.

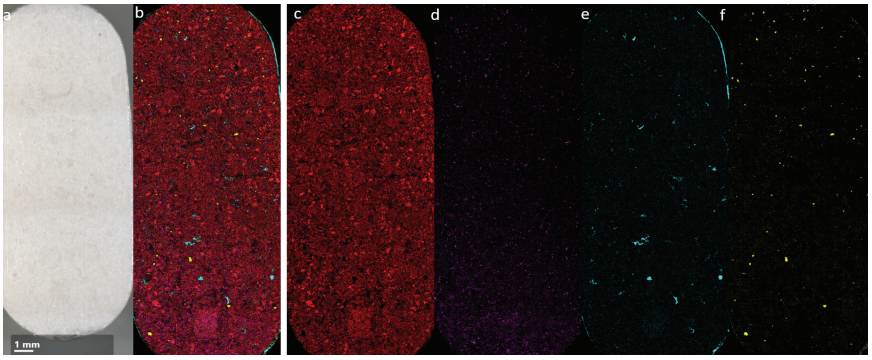

Figure 3. (a) Visible image of microtomed printed side of tablet facing up. (b) The composite image with all the constituents of the printed side of the tablet facing up. (c-f) The individual chemical map of acetaminophen (c), cellulose (d), hydroxyethyl cellulose (e), and starch (f). The scale bar is 1 mm long.

Fast Screening and Detailed Analysis

Since the 8700 LDIR enables rapid imaging across an entire tablet surface, samples can be quickly screened in several minutes. Alternatively, a single sample can be quickly analyzed in detail. For example, it took only 29 minutes to analyze the tablets shown in Figures 2 and 3 (left). Each image 19.35 mm × 7.77 mm in size and was scanned at 10 µm pixel size, with four constituents being mapped.

Example Tablet Analysis

Over-the-counter extended release caplets were analyzed. They contained acetaminophen as the active ingredient as well as several common excipients, including cellulose, starch and hydroxyethyl cellulose.

The caplet was sectioned with a microtome and then imaged (Figure 1). This allowed the constituent distribution to be mapped. The analysis revealed that the tablet had two horizontal layers. The interface between the two layers in the tablet is evident in Figure 1b. The relative distribution of the acetaminophen, starch, and hydroxyethyl cellulose constituents can be easily seen in those layers.

The tablet was further imaged with first the unprinted side facing up (Figure 2), and then the printed side (Figure 3). These images show the differences in the distribution of the constituents, particularly the starch and hydroxyethyl cellulose.

Constituents such as hydroxyethyl cellulose and sodium starch glycolate are often used to control the rate of dissolution of the tablet. The chemical images of the constituent distribution show that the printed side layer, with more hydroxyethyl cellulose (dissolution retardant), is a sustained release layer and the unprinted side, with more starch, is the immediate release layer.

For more information, visit:
www.agilent.com/chem/8700-ldir

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