

Rapid Discrimination and Classification of Polymorphs Using the Agilent 8700 Laser Direct Infrared (LDIR) Chemical Imaging System



Introduction

It is necessary to characterize polymorphs of pharmaceutical active ingredients (APIs) because different crystal forms of the same molecule can show widely varying physicochemical properties, such as solubility, thermodynamic stability, bioavailability, and therapeutic efficacy. Understanding the conditions and chemistry of polymorph formation is essential for consistent drug performance and product quality control.

Infrared (IR) spectroscopy is often used to identify different polymorphs. The Agilent 8700 LDIR Chemical Imaging System can rapidly identify and discriminate between polymorphs in solid dosage forms.

Key benefits of the Agilent 8700 LDIR Chemical Imaging System for polymorph analysis

Fast classification and discrimination

The Agilent Clarity software automatically allows users to create methods to distinguish between each polymorph and excipient in a mixture. By collecting information at only significant wavelengths, the 8700 LDIR greatly reduces the time required to spatially image the distribution of the ingredients.

Rapid analysis and imaging

Speed of analysis is important in the study of polymorphs as conversion can occur in minutes and following the conversion requires a rapid imaging method. The 8700 LDIR enables the real-time visualization of the conversion before a final equilibrium state is reached.

Excellent resolution

The 8700 LDIR has the unique ability to measure megapixel Attenuated Total Reflection (ATR) images at down to a pixel size of 0.1 micron. This makes it easy to see crystal growth. Being able to observe large areas at high resolution in reflectance mode enables a more statistically accurate representation of polymorph formation and conversion.

Easy to use instrument and software

High spatial resolution images can be obtained for either a full tablet scan or a detailed study of a small sample area without changing any instrument optics or objective lens. The unique Agilent 8700 LDIR point scanning mode allows you to define the spatial resolution before starting the data collection.

Relative quantification

Identification of sample constituents by the Agilent Clarity software also enables relative amounts of polymorphs and other ingredients such as excipients to be determined without developing separate quantitative methods.

Analysis example: LDIR imaging of carbamazepine polymorphs

Carbamazepine (CBZ) is an anticonvulsant and mood stabilizing drug [1] that is known to exist as different polymorphs. Of the four crystal forms (III > I > IV > II; room temperature stability order), only form III is known to have therapeutic effects [1,2]. Detecting and understanding the formation of non-therapeutic polymorph I is essential when developing CBZ solid dosage forms. Forms I and III can be rapidly distinguished and mapped using LDIR imaging.

Library spectra are first acquired for the two polymorphs and the cellulose excipient in the sample. The Agilent Clarity software then creates a rapid imaging method by selecting the key diagnostic wavelengths for each of the three constituents (Figure 1).

The method can then be used to image CBZ polymorphs across an entire tablet.

Images of 13 mm tablets with 10 μm pixel size, obtained in 27 minutes are shown on in Figure 2. Two formulations were studied: (1) 5.2% form I, 15.4 % form III, and (2) 15.3 % form I, 5.5 % form III, by weight, with the remainder being cellulose. The measured surface concentrations, in which the density of the polymorphs is not considered, showed excellent correlation with the known percentages by weight. The chemical distribution of the three major constituents can be individually displayed, as shown in Figure 3.



The Agilent 8700 LDIR Chemical Imaging System

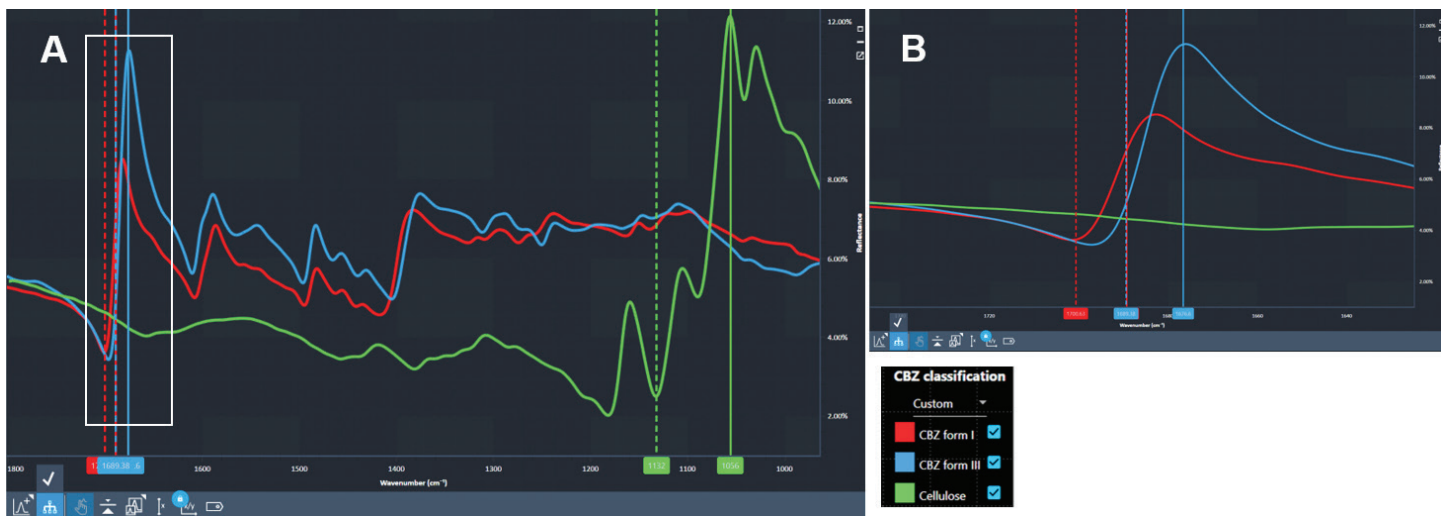


Figure 1. (A) Library reflectance spectra of pure constituents (CBZ form I, form III, and cellulose) – peak (solid line) and baseline (broken line). Positions for each constituent are automatically selected and form the basis for the image. (B) The white inset region in 1A is expanded and shows the frequencies selected for classification of forms I and III.

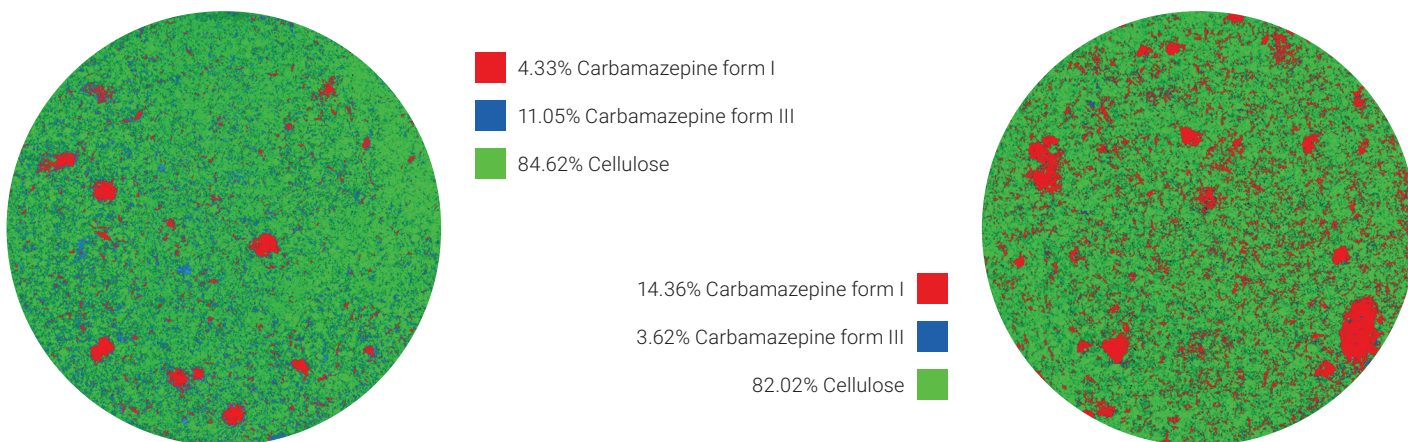


Figure 2. Classification image of a 13 mm tablet showing the distribution of Carbamazepine forms I & III and cellulose at 10 μm pixel size. At 10 μm pixel resolution, classification analysis for the whole 13 mm diameter tablet sample required only 27 minutes.

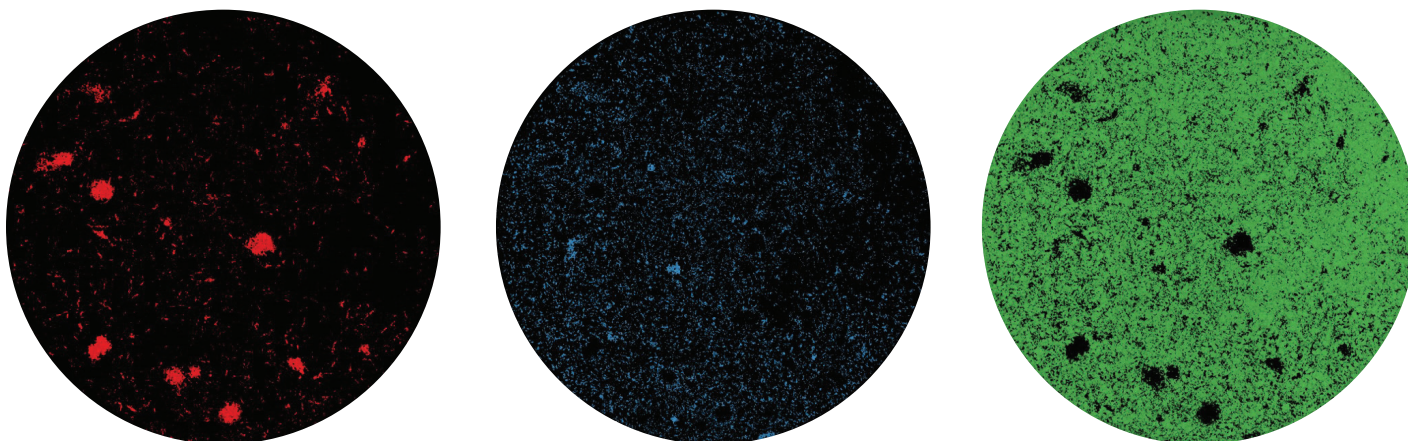


Figure 3. From left to right: Individual chemical maps of CBZ forms I & III and cellulose in the tablet.

References

1. Czernicki, W; Baranska, M. Carbamazepine polymorphs: Theoretical and experimental vibrational spectroscopy studies. *Vibrational Spectroscopy*. **2013**, Vol (65) 12-23.
2. Grzesiak, AL; Lang, M; Kim K; Matzger, AJ. Comparison of the four anhydrous polymorphs of carbamazepine and the crystal structure of form I. *J. Pharm. Sci.* **2003**, Vol. (92) 2260-2271

www.agilent.com/chem/8700-ldir

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