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Infrared hyperspectral imaging for qualitative analysis of pharmaceutical solid forms

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Abstract

A multi-spectral imaging spectrometer records simultaneously spectra and spatial information of samples. The infrared (IR) imaging system used was the Hyperion 3000 microscope (Bruker Optics) equipped with a focal plane array (FPA) detector. The detector allows creating a 64×64 pixels image. For each pixel, a complete spectrum is acquired, which means that an IR image is in fact a data cube. Two methods for qualitative analyses of the data cube were applied: peak height and unfold principal component analysis (PCA). These methods were performed on two different pharmaceutical problems: the first one was the analysis of a contamination on the surface of a pharmaceutical solid dosage form and the second one was a set of six images of intact tablets with different dissolution properties. On the first data set, IR imaging and chemometrics identified the contamination (a concentration of wet dye). The imaging method applied on the second set allowed the determination of the main cause of the dissolution problem, which was the surface distribution of magnesium stearate. This study shows that infrared imaging can be useful for qualitative analysis and troubleshooting of pharmaceutical solid forms.

Keywords: Infrared imaging; Focal plane array detector; Unfold PCA; Solid pharmaceutical; Dissolution properties; Troubleshooting

1. Introduction

Infrared (IR) spectroscopy is in evolution: instrumentation and data treatment are constantly improving. When a sample is analyzed by IR spectroscopy, its homogeneity is an important issue. A spectrometer integrates the spatial information and in case of the analysis of a solid form, the use of a mean spectrum on a surface can be a drawback. For example, in the pharmaceutical industry it is important to map the distribution of the active ingredients and the excipients in a tablet [1]. Therefore, more and more studies deal with spectroscopic imaging [2,3].

Infrared multi-spectral imaging is a recent development that combines the chemical information from spectroscopy with the spatial information [4]. In principle, it is possible to collect multi-spectral images with simple point detectors, i.e. the classical mapping with IR microscopes. However, the array detectors measuring simultaneously with multiple detector elements reduce the recording time, provide uniform background and improve the signal to noise ratio [5]. Fig. 1 presents the general principle of an IR imaging system and the structure of the data obtained.

A FPA is an optical detector placed at the focal plane of a spectrometer and it can be manufactured to be sensitive to ultraviolet, visible, near infrared or infrared radiations. Recent developments in optics allow the production of cooled and uncooled FPAs with different numbers of pixels from 64×64 up to 1024×1024 pixels and a different spectral ranges of detection (from 1 to 12 μm) [6,7]. The mercury cadmium telluride (MCT) detector has become the dominant FPA in the IR region because of the coverage of the entire IR range.

By using IR imaging, a new type of data structure needs to be analyzed: an IR data cube. A monochromatic image can be presented as a two dimensional $n \times m$ array describing the distribution of the light intensity where n and m are the numbers of digitalization steps, i.e. pixels, along the x and y directions. An infrared hyperspectral image is defined by

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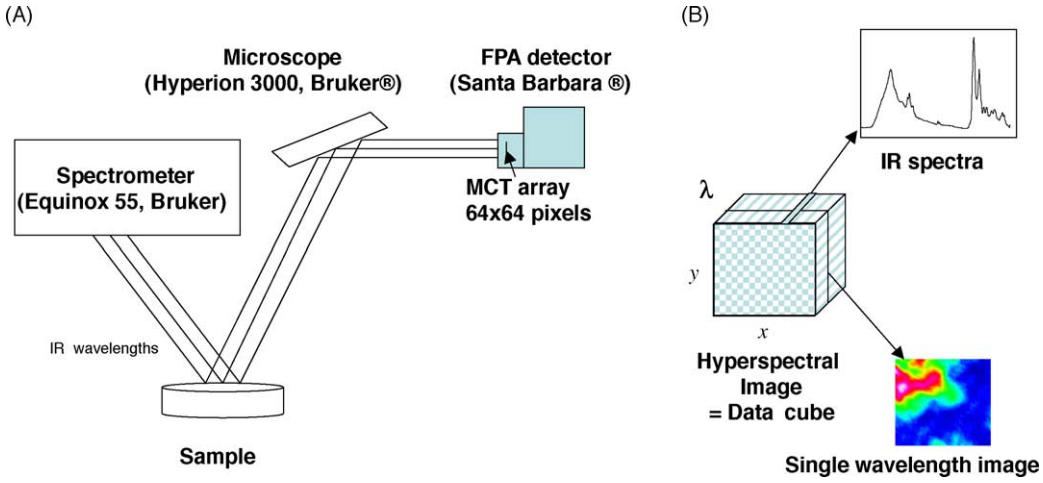

Fig. 1. Description of the infrared imaging system: (A) instrumentation; (B) data structure.

at least 50 planes [8]. In our study, 376 wavelengths were recorded, that means the result is a 3D $n \times m \times 376$ array (Fig. 1).

The aim of this paper is to present methods for the qualitative analysis of an IR image, i.e. concatenation of data cubes, peak height and unfold principal component analysis. We will discuss also how IR imaging can be a new technology to analyze pharmaceutical solid forms. Two examples will be described: the identification of a contamination on the surface of a tablet and the explanation of dissolution problems by analyzing the surface of a second type of tablets.

2. Materials and methods

2.1. Pharmaceuticals samples

2.1.1. Analysis of a contamination

One tablet with the presence of a blue spot on the surface was analyzed. Three pure products were analyzed as references: the active ingredient (a molecule of the benzodiazepine family), the dye (indigo carmine) and the placebo (mixture of all of the excipients without the active ingredient: avicel, indigo carmine, magnesium stearate).

2.1.2. Dissolution problems

Six samples were analyzed: three of them had 'good' dissolution properties and three failed the dissolution test (the 'bad' samples). Several ingredients were used as references: avicel PH101, the active ingredient, magnesium stearate, and poloxamer 188.

The dissolution testing was accomplished after the IR imaging measurement, using the Sotax Dissolution Tester AT 6 and AT 7 smart paddle stirrers (Sotax AG, Allschwil, Switzerland) in artificial gastric juice (pH 1.2, 37 °C, stirred at 75 rpm). The Perkin-Elmer Lambda 40 UV spectrophotometer (Perkin-Elmer AG, Hünenberg, Switzerland) was utilized.

2.2. FT-IR measurements

An Equinox 55 spectrometer (Bruker, Ettlingen, Germany) coupled with a Hyperion 3000 microscope equipped with a 64×64 MCT FPA detector were used to acquire the IR spectra between 3900 and 900 cm^{-1} at 16 cm^{-1} resolution (i.e. 376 data points) under N_2 purge. The binning function (i.e. pixels are grouped together) was applied to improve the signal and finally an image of 16×16 pixels was acquired. The number of scans was 20 and the surface analyzed by one FPA measurement was a 270 μm × 270 μm area.

2.3. Chemometrics methods

2.3.1. Data pre-treatments

The spectra of the two data sets (contamination and dissolution problems) were normalized with the standard normal variate (SNV) method, i.e. the spectra were mean centered and scaled to unit variance by spectrum. The spectral data are reduced and centred [9] by the use of the following calculation:

$$\mathrm{SNV}_i = (x_i - \bar{x}) \Big/ \sqrt{\frac{\sum_i (x_i - \bar{x})^2}{(w-1)}} \quad \text{for } i \in [3900\,\mathrm{cm}^{-1};\ 900\,\mathrm{cm}^{-1}].$$

where x_i is the $\log(1/R)$ value at the wavelength i, w the number of wavelengths, $\bar{x}$ is the mean of the $\log(1/R)$ values (on each segment) and SNV_i is corrected $\log(1/R)$ value at the wavelength i.

For the second set (dissolution problem), the Savitszky-Golay [10] method was applied to correct the baseline shift (filter length: 19 points and filter order: 3) after the normalization.