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Increasing the spatial resolution of near infrared chemical images (NIR-CI): The super-resolution paradigm applied to pharmaceutical products

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ABSTRACT

Near-infrared chemical imaging (NIR-CI) is widely used in the pharmaceutical industry not only to provide the concentration of a compound of interest but far more often to obtain the spatial distribution of different ingredients within the considered sample like a single tablet. For such sample characterization, having a high field of view is of major interest. As well as their high field of view, recent NIR-CI spectrometers have the ability to acquire thousands of spectra in a very short time due to focal plane array detector they use. Nevertheless, the spatial resolution is often limited which implies that generated chemical images are often biased. In view of this it was deemed appropriate to develop a new chemometrics methodology called "super-resolution" in order to increase the spatial resolution of spectroscopic images. The main idea is the fusion of several low-resolution images of the same sample observed from different point of view in order to generate one higher-resolution image. We offer here an objective and quantitative evaluation of the super-resolution concept with applications on pharmaceutical solid samples.

1. Introduction

In the pharmaceutical industry, as in many other sectors, near infrared spectroscopy has become an important tool for the characterization of raw materials, final or in-process products. This molecular spectroscopy is generally chosen for its speed, its low cost and its non-destructive characteristic towards the analyzed sample. Moreover, it allows analyzing samples as they are, without preparation, and even sometimes directly through their final packaging. It is a fact that near infrared spectroscopy is a valuable tool in global analysis for quantification and classification purposes. Moreover, the development of chemical imaging (CI) has gifted this spectroscopy an additional dimension. Chemical imaging systems effectively complement chemical identification by acquiring spatially located spectra that enable visualization of chemical compound distributions. It is obvious that such spectroscopic techniques provide relevant information about the distributions of excipients and active pharmaceutical ingredient. Indeed, it is a good way to assess the product's behavior during manufacture and more importantly its physical attributes such as dissolution properties or stability. Near infrared spectroscopic imaging is a real tool for enhancing drug quality and understanding process.

This increasing interest in the use of NIR-CI in pharmaceutical industry can be explained by instrumental developments made around the 2000s. Prior to this period, the point mapping technique is the most used to generate NIR chemical images. A classical near infrared spectrometer is thus coupled with a microscope allowing the spectral acquisition on a few micrometer size zone on the sample surface. A moving stage is also necessary to obtain the systematic and sequential spectral acquisition all over the sample region of interest defined by the user. Considering usually large sample area we want to probe (few mm^2 on tablets for example), even a few seconds acquisition time per spectrum induces several hours of acquisition due to thousands of positions to consider. Therefore we can see that, at this date, such methodology is rather limited for a real analytical use in the pharmaceutical industry. Everything changes around the 2000s, with the arrival of multi-channel focal plane array detector (FPA) newly installed on commercial near infrared imaging systems. It is composed of several thousand elements forming a matrix of pixels with which it is now possible to acquire simultaneously all the spectra of the sample region of interest. Even if the point mapping technique can have advantages, the strongest argument in favor of this wide field imaging system is the real faster acquisition time, making it an instrument of choice for the PAT initiative (process analytical technology) and pharmaceutical Quality by Design.

For pharmaceutical imaging applications, it is essential that we obtain high resolution (HR) images. An HR image, with its high pixel density, can effectively present many details about the considered sample. We have then a better vision of the reality and therefore

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better interpretations and knowledge of the chemical system. We can even say that using a low resolution image is risky because it can give us a biased vision and then wrong estimations of chemical and physical properties. In this way, an FPA imaging system does not solve all problems since the desire to have a rather high field of view (often several mm^2) led to observe an important sample surface per pixel (often higher than several hundred μm^2). The aim of the presented work is to propose a new methodology in order to increase the spatial resolution and pixel density of near infrared chemical images while keeping the original field of view of the considered spectrometer.

In general, the first way to increase the resolution of an imaging device is an instrumental one, whereby we try to reduce the pixel size of the detectors. Nevertheless, pixel size reduction decreases the signal to noise ratio. A second way to increase the resolution is to expand the FPA chip size i.e. having always a higher number of pixels. Unfortunately, this solution is always more expensive. It is also more difficult to obtain a uniform illumination of the detector. On top of that, optical aberrations are more important. All those solutions present significant constraints and it is in that sense that we propose here a signal processing concept called super-resolution (or superresolution) in order to increase the spatial resolution while maintaining our actual imaging spectrometers.

Super-resolution is a discipline of the signal processing research field. It is defined by the use of image processing methods in order to overcome limitations of optical systems [1-3]. The concept of the proposed super-resolution algorithm is the fusion of several low-resolution (LR) images of the same sample observed from different point of view in order to generate one higher-resolution image [4-6]. Tsai et al. was the first to demonstrate that a high resolution image can be obtained from several under-sampled low resolution images with relative sub-pixel moves between them [7]. Recently, we were the first to develop the super-resolution concept for molecular spectroscopy and more precisely for Raman and mid-infrared ones [8,9]. It is now a good opportunity to evaluate the potential of super-resolution in near infrared imaging for the characterization of pharmaceutical products.

2. Materials and methods

2.1. Materials and sample preparation

This work required two different kinds of samples. The first one is considered as an ideal sample. It is spatially and chemically well defined. These characteristics are very important since the chosen sample has first enabled us to propose a methodology for the evaluation of the intrinsic spatial resolution of the imaging spectrometer. Moreover, it gives us a quantitative estimation of the spatial resolution improvement when the super-resolution algorithm is applied on low resolution images. We chose here the well known "1951 USAF resolution target" as ideal sample. It is a resolution test pattern conformed to the MIL-STD-150A standard, set by US Air Force in 1951. Many chrome metal coating patterns are observed on the surface of a soda-lime glass. It is particularly well suited for such NIR experiments because contrasted images are obtained due to the high reflectivity difference between metal and glass. Moreover the reflectivity remains approximately constant on the whole spectral range enabling the evaluation of the spatial resolution for various wavelengths. As we can see on Fig. 1, the pattern consists of groups of three bars with dimensions going from large to small. The largest groups, forming the first layer, are located on the outer sides. The smaller layers repeat the same pattern but are progressively smaller toward the center. In this way, it is possible to observe bars with a width decreasing from 500 μm to 0.78 μm. More details on the resolution target can be found elsewhere [9].

The second type of sample corresponds to real pharmaceutical samples. Two solid forms are investigated. First, a powder mixture of cellulose and talc is used as representative of raw materials. Second, a tablet containing caffeine and lactose is selected as representative of a final product.

2.2. Spectral acquisition and LR images generation

A Spectral Dimensions Sapphire NIR-CI 2450 spectrometer (Malvern Instruments, Olney, MD, USA) equipped with an InSb focal plane array

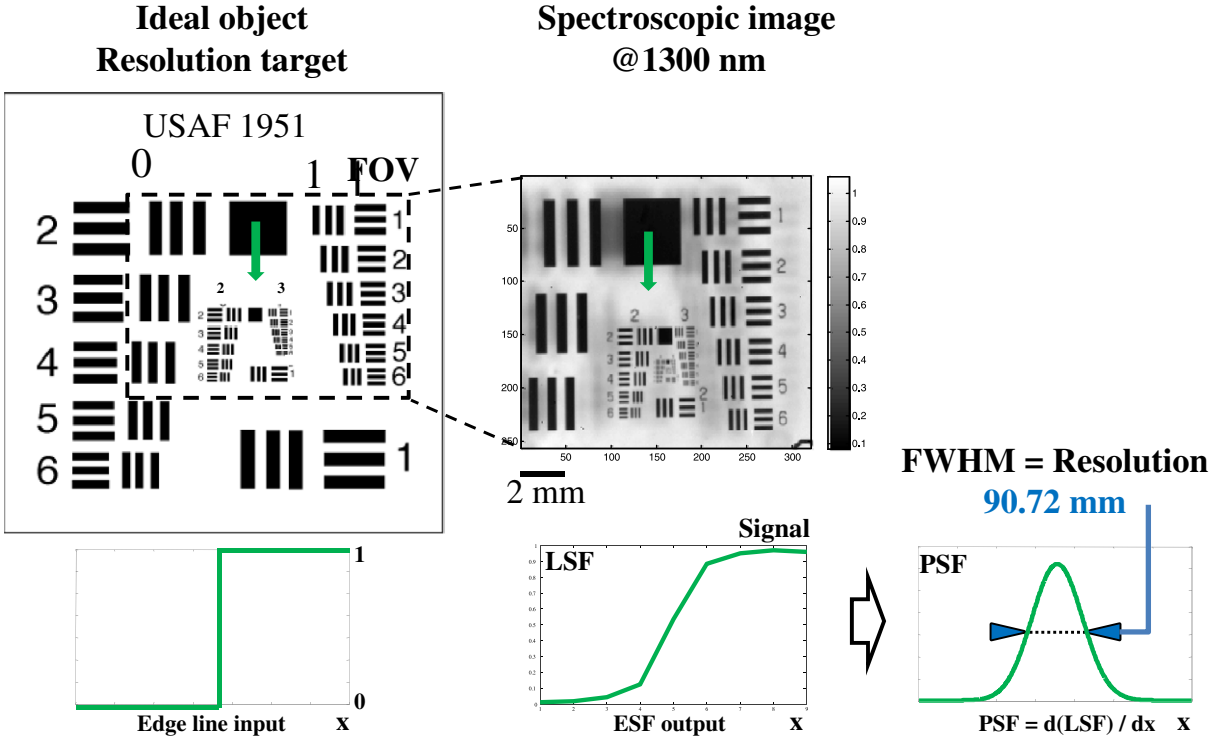

Fig. 1. The resolution target and the "step-edge" method.