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Detecting small amounts of multiple API polymorphic forms in powder blends

Chemical sciences

Introduction

The stability, bioavailability and processability of an active pharmaceutical ingredient (API) are key to a candidate molecule's ability to be developed into a commercially viable product.

Different drug polymorphs can vary markedly in properties such as their flowability, dissolution rate, solubility, and stability.

Characterising the different polymorphic forms of a drug and selecting the optimum polymorph for drug product development have become important considerations in this process.

From ensuring the correct polymorph remains throughout a product's shelf life, to aspects of patent law as a means of both extending and circumventing existing patents, increasing amounts of money and resources are being devoted to characterising polymorphism.

Current methods for determining polymorphism can be expensive, resource-intensive and require expert users to operate equipment and interpret data. Furthermore, contemporary techniques are often limited by their sensitivity - and struggle to determine the presence of polymorphs at low concentration. Particularly in complex blends of material, such as tablets.

Case study: Determining the relative amounts of two polymorphic forms in a generic drug product

Renishaw's RA802 Pharmaceutical Analyser was used to detect small amounts of different polymorphic forms (form I and form II) of an active pharmaceutical ingredient (API) in a generic drug powder.

The generic product is intended to contain only the off-patent form of the API (form I). Form II is the patented form of the API and is owned by the innovator. Any presence of this polymorphic form in the generic product may, therefore, constitute patent infringement. Thus, a method capable of detecting very small amounts of form II - confirming that no detectable levels are present - is vital to ensure that the generic product can be successfully brought to market.

The Renishaw RA802 Pharmaceutical Analyser

The RA802 Pharmaceutical Analyser ensures:

- high specificity enabling polymorphic forms of the same API to be distinguished
- high spatial resolution and sensitivity so even small amounts of API are detected

Conventional techniques for polymorphic detection, such as XRD, do not provide the same sensitivity to small amounts of different API polymorphs within a blend or formulation.

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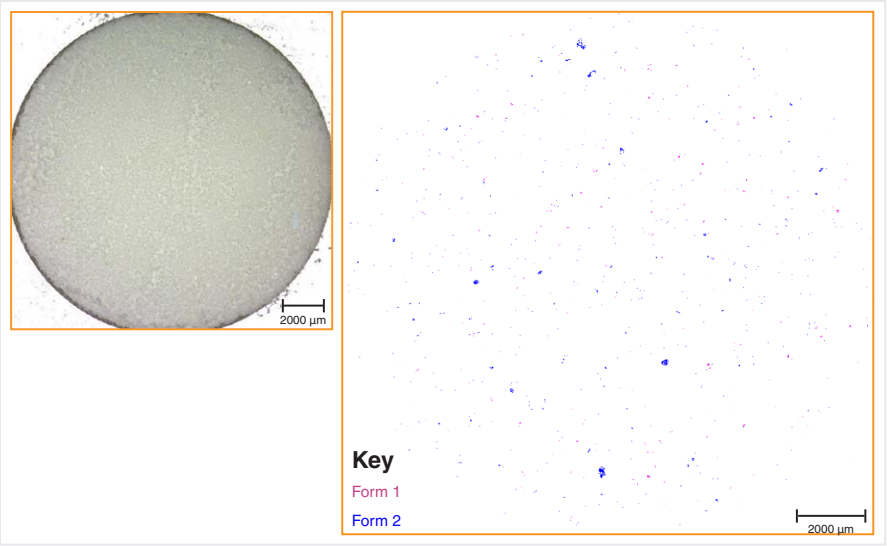
Screening the whole sample for API forms

The image below shows the presence of both polymorphs (form I and form II) of the API in the analysed powder blend. Although only small amounts of form II are present, the high spatial resolution of the system enables this polymorph to be detected and its location established.

The image of the whole powder sample comprised over 2.5 million pixels.

- Form I was detected in 8000 pixels (0.3 % of the total pixels)
- Form II was detected in 3200 pixels (0.1 % of the total pixels).



Macro white light image of powder blend in circular well (analysed area shown in orange) (left) and Raman chemical image (right) showing the presence of both API forms in the analysed sample.

It is clear that the detection limit of such API forms can be significantly lower than 0.1 % using the RA802 Pharmaceutical Analyser. The presence of a material within a single image pixel, as small as 1 µm in size, can be determined when the entire image may be millions of pixels in size.

Typically, these types of drug products are effectively homogeneous on the length scale of larger than tens of micrometers but exhibit local inhomogeneity on length scales of micrometers. Raman imaging, whereby many Raman spectra can be recorded from millions of different spots within a sample, can investigate this homogeneity. Each spectrum is recorded from a sample size of the order of low single digit micrometers, and hence can probe the local inhomogeneity.

In this example, some of the API is detected in as little as one isolated pixel within the image, corresponding to an area of 10 μm^2. It is conceivable therefore, that a detection limit as low as 4×10^{-5} (0.00004 %) of the total pixels - one pixel in the whole image - would be feasible. This figure could even be lower at higher spatial resolutions.

The RA802 Pharmaceutical Analyser can be used to analyse a range of pharmaceutical samples, such as powder blends and tablets, to screen for the presence and form of APIs. This system combines StreamLine™ fast imaging technology with LiveTrack™ focus tracking technology to rapidly analyse large areas of non-flat samples. Determining the API form(s) present at various stages in the manufacturing process can be used, for example, to avoid patent infringement and to understand polymorphic conversion under different storage conditions.

A range of related Renishaw literature is available. Please ask your local Renishaw representative for more information.

Renishaw. The Raman innovators

Renishaw manufactures a wide range of high performance optical spectroscopy products, including confocal Raman microscopes with high speed chemical imaging technology, dedicated Raman analysers, interfaces for scanning electron and atomic force microscopes, solid state lasers for spectroscopy and state-of-the-art cooled CCD detectors.

Offering the highest levels of performance, sensitivity and reliability across a diverse range of fields and applications, the instruments are designed to meet your needs, so you can tackle even the most challenging analytical problems with confidence.

A worldwide network of subsidiary companies and distributors provides exceptional service and support for its customers.

Please visit www.renishaw.com/Raman for more information.