

## **How Synchrotron Radiation X-ray Powder Diffraction (SR-XRPD) compare with the Near Infra-Red Spectroscopy (NIRS) technique in pharmaceutical technology?**

The combination of NIRS with chemometric methods<sup>1</sup> has enabled the qualitative and quantitative analyses of physical and chemical properties of chemical species and polymorphic forms in mixtures. NIRS analyses are usually fast, cheap, non-destructive and require no or little sample preparation. NIRS is therefore ideal for routine analyses and in-line monitoring in industrial environments. However, NIR spectra of mixtures typically contain broad, overlapping bands that cannot be associated to an individual sample component. Therefore, no matter what chemical or physical property of the sample needs to be monitored, the identification and quantification of components in a mixture require the comparison of the measured NIR spectra with some appropriate calibration sets (so-called spectral library) and the application of complex chemometrics techniques<sup>2,3</sup>. An exhaustive spectral library typically requires the preparation and measurement of hundreds of samples containing varying compositions of the components of interest, covering the whole range of concentrations to be measured. This library must be established for each instrument, since the NIR spectra are strongly instrument dependent, or require complex calibration transfer procedures to be applied<sup>4</sup>.

In the case of qualitative analyses, the correct identification of components requires that all these components have been effectively included in the calibration set. Additionally, for a successful quantification, an adequate quantitative model must be established, which predicts the property of unknown mixtures from their NIR spectra. Developing such a model requires appropriate reference methods to evaluate the property of samples which will be used in the chemometrics computation<sup>4</sup>.

XRPD is a direct objective analytical method for structural and microstructural analyses of virtually any kind of material. 'Objective' means that it does not require reference diffraction patterns, apart from the calibration of the photon energy (always necessary), the Instrumental Resolution Function (for microstructural analysis) or absolute (i.e. not % wt) quantitative phase analyses. The recent development in instrumentation, computer technology and powder diffraction experimental techniques [e.g. anisotropic thermal expansion<sup>5</sup> and texture methods<sup>6</sup>] and methodologies [e.g. global optimization techniques<sup>7</sup>; resolution bias algorithm<sup>8</sup>; charge flipping<sup>9</sup>; combined XRPD-electron diffraction<sup>10</sup> or XRPD-Raman (or IR) spectroscopy<sup>11</sup>; quantitative phase analysis based on whole-pattern evaluation with or without the knowledge of a structural model<sup>12,13</sup>; advanced whole-patterns microstructural analyses method<sup>14</sup>] have all contributed to its success and have together upgraded XRPD from a support technique to a fundamental one. Furthermore, the recent development of total scattering techniques (i.e. techniques that interpret both Bragg and diffuse elastic scattering) has extended the use of

powder diffraction to nano- or non-crystalline (i.e. liquid and amorphous) materials<sup>15-17</sup>. XRPD is, therefore, unanimously considered the gold standard technique for the identification and quantification of solid forms (polymorphs, solvated, hydrates, salts, cocrystals and amorphous<sup>18</sup>).

The advent of synchrotron radiation has caused powder diffraction to enter a new era of development<sup>19</sup>. The several experimental limitations of conventional XRPD have been overcome by the use of synchrotron radiation thanks to its superior characteristics:

- High photon wavelength resolution ( $\Delta\lambda/\lambda$  better than  $2 \cdot 10^{-4}$ )
- Highly collimated (residual divergence less than  $20 \mu\text{rad}$ ) and intense ( $> 10^{13}$  photon/sec) photon beam
- Tunable photon energy in a large interval (typically 5 to 40 keV) ideal to perform anomalous scattering experiments, collect fluorescence-free XRPD data and better diffraction peaks separation.
- Angular (FWHM) resolution better than  $0.01^\circ 2\theta$  obtained with new generation solid state microstrip detectors (MYTHEN II detector<sup>20</sup> developed at the Swiss Light Source and available to Excelsus) and down to  $0.002^\circ 2\theta$  using multicrystal analyser detectors
- d-spacing resolution better than  $0.35 \text{ \AA}$
- Debye-Scherrer (transmission) as well as Bragg-Brentano (reflection) geometries
- Reduced preferential orientation effects due to transmission geometry and very high sample spinning ( $>10 \text{ Hz}$ ).
- Ultra-fast data acquisition (milliseconds scale) for efficient, dose-controlled and time-resolved XRPD
- Very high signal-to-noise and signal-to-background
- Ultra high counting statistics (millions of counts) in few seconds

These peculiar characteristics of SR-XRPD together with the application of the above mentioned modern powerful methodologies for structural solution and refinement, quantitative phase and microstructural analyses make SR-XRPD the ideal reference method for supporting NIRS spectral libraries and quantitative models construction.

Furthermore, when NIRS analyses fail in the identification or classification of a material due to an unrecognizable NIR spectrum, SR-XRPD can help identifying the origin of the unexpected variation.

**Why not always using SR-XRPD?** Because SR-XRPD, although now of much easier and fast access, remains not suitable for routine and massive at-line monitoring applications.

In summary, NIRS and SR-XRPD are complementary techniques:

NIRS is a technique of medium accuracy (detection level of typically 2-3 %wt) suitable for at-line fast routine qualitative and quantitative analyses. It requires a time-consuming preliminary

identification of all chemical species and polymorphic forms to be measured, followed by extensive work to establish a spectral library and to develop a quantitative model. Any species or form which has not been included in this calibration work may not be detected or quantified properly. Such a massive preliminary work is worthwhile for routine NIRS measurements but not for accurate measurements during technical development and for investigations following a deviation in routine manufacturing.

SR-XRPD, is a high-accuracy (detection level typically better than 0.1% wt), high-angular (FWHM) and d-spacing resolution technique (better than  $0.01^\circ$  in  $2\theta$  /  $0.5 \text{ \AA}$  d-spacing)<sup>20</sup>, suitable for the detection and identification of chemical species and polymorphic forms not necessarily known previously. SR-XRPD requires complex instrumentation<sup>21</sup> and strong know-how<sup>22-24</sup>, making it not suitable for in-line routine monitoring. Access and operation of synchrotron radiation based powder diffraction instrumentation has traditionally been difficult, expensive and characterized by unacceptable waiting times. However Excelsus mission is to provide easy access to this technique at very affordable price conditions.

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