

SAM-Spec® Spectroscopy used to measure simultaneously API concentration and Particle size distribution – Example of application on drug layering process.

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1 Introduction

In the production of pharmaceutical products, active pharmaceutical ingredient (API) concentration, homogeneity and particle size distribution (PSD) are the main critical quality attributes of the product throughout the production. Hence, the importance to non-destructively quantify the content of the active ingredients as well as the overall particle size distribution throughout the granulation process.

Since most pharmaceutical ingredients and their fillers show absorption bands in the Near InfraRed spectral range of 900nm – 1700nm and sometimes up to 2200nm, using Near InfraRed spectroscopy and based on the Lambert-Beer theory, it is possible to achieve quantification of API content in the drug product.

However, variability in the granules density and PSD are also reflected in the optical scattering changes of the NIR absorbance spectrum. They are on the basis of challenges that quantitative analysis of the active ingredient by NIR faces, especially when dealing with low API strengths. Various approaches to achieve absolute quantification of both chemical and physical properties exist and they mainly involve the determination of absorption and scattering parameters of the target sample. This is the principle used by the SAM-Spec® spectroscopic system that allows the separation between chemical – absorption spectra and physical - scattering spectra. This technique uses several measuring locations (e.g. 4 locations) throughout the sample in order to evaluate its optical properties [1]. The signal obtained is therefore a 2D signal with at least 4 spectra taken at different positions from the irradiating point.

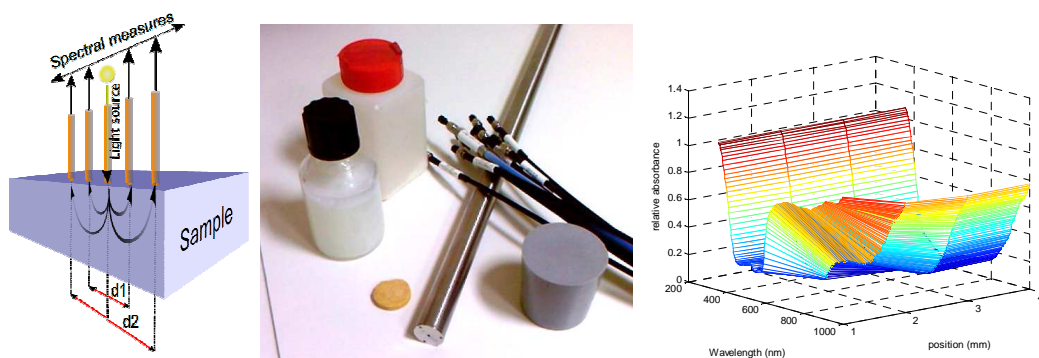


Figure 1 Principle of Sam-Spec® (left); Probe (middle; 2-D data generated for one sample (right).

In this work, advantages of using SAM-Spec® probe provided by Ondalys company are shown to demonstrate its capability to provide non-destructive, off-line or online, measurements of API content as well as PSD throughout the drug layering process of a pharmaceutical drug product.

2 Material and method

2.1 Measuring procedure

Sample were measured using an ASD spectrometer (350nm-2500nm) controlled by a specific interface able to deal with the 4 measuring position. 270 samples of GSK granules collected at Flamel Technologies, Pessac during drug layering and polymer coating, were evaluated using the SAM-spec probe.

Only 72 samples had been measured in the lab for API content and PSD (d10, d50 and d90).

62 of these samples have been used for SAM-spec calibration model and test (10 samples were left because there were not enough product to perform spectral measurement).

2.2 Modelling approaches

Prediction model for PSD and API were obtained using N-PLS [2] on the 2D data. Models were calculated using Matlab and PLS toolbox.

PSD model were obtained using the visible range of the spectra. For API prediction two different spectral (UV-VIS and NIR) range were tested and compared

3 Results

3.1 PSD prediction:

The calibration model determination coefficient for the D10¹ using SAM-spec data is $R^2 = 0.89$. However the model performance decreases in test to $R^2 = 0.81$ but it is still acceptable. The error on the SAM-spec measurements of D10 is represented by the Standard Error of Prediction SEP = 9.01 micron.

The same level of performance ($R^2 \sim 0.89$) can be reached for the prediction of the other part of the particle size distribution D50, D90.

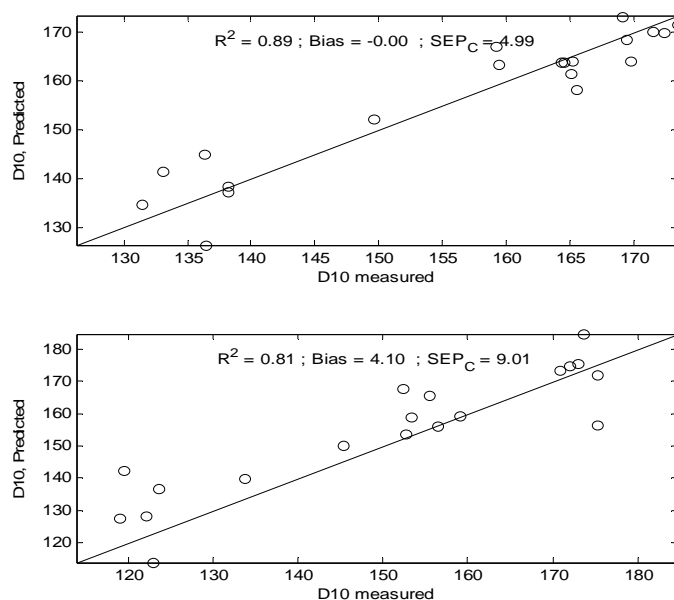


Figure 2 Prediction of D10 in calibration (top) and prediction (bottom)

¹ The definition of d10 is: that equivalent diameter where 10 mass % (of the particles) of the powder has a smaller diameter (and hence the remaining 90% is coarser). The definition of d90 can be derived similarly.

3.2 API prediction , Model based on spectra collected n NIR region:

N-PLS model was built using 5 latent variables. Result for calibration and prediction are very good ($R^2 > 0.9$). A limit of prediction is appearing near 5: the predictions are equal to 0 when API concentration goes below 5. This result can be improved by increasing the ratio signal/ noise (examples: using a more powerful halogen lamp or testing the probe with FTNIR)

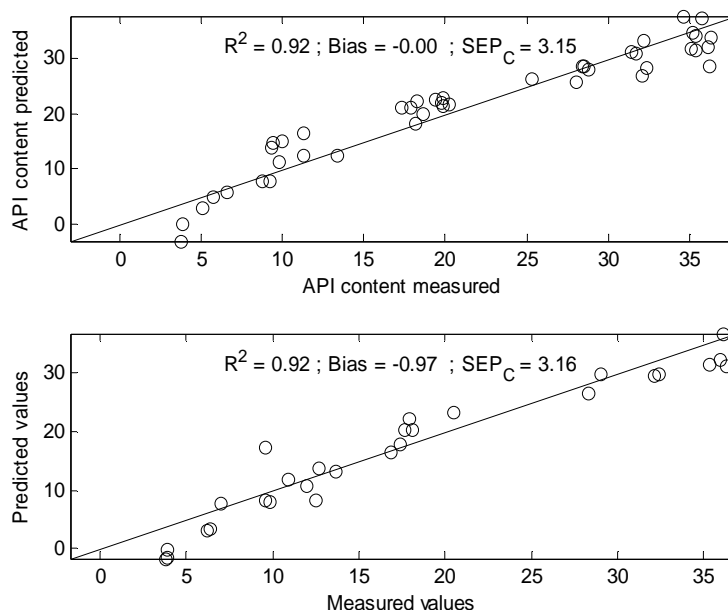


Figure 3 : API Prediction plot calibration and prediction

3.3 API Prediction Model based on spectra collected in UV-VIS and NIR<1000nm :

The model performance increases while the detection threshold of 5 disappears, demonstrating improved accuracy. This result can be explained because the region used for calibration has a lower absorption and higher scattering. Therefore photons can travel a longer time in the sample and gives more precise information regarding the chemical structure of the sample.

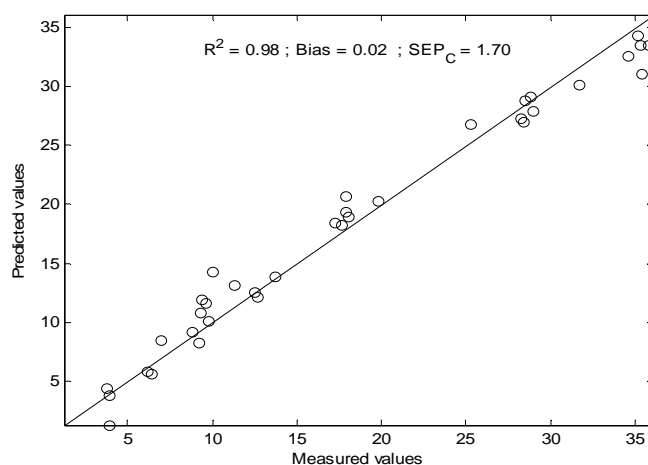


Figure 4 : API Prediction plot.

4 Conclusion

SAM-Spec® demonstrated the ability of predicting physical parameters and chemical parameters.

Best performance for API prediction was obtained in the visible/NIR region. Physical parameter (d10, d50) were predicted with an interesting performance ($R^2=0.82$) but lower than for API ($R^2=0.95$).

The study has demonstrated the main interest of SAM-Spec technology: being able to use the classical tool of NIR spectroscopy but with the possibility of predicting simultaneously both physical properties and chemical concentration of a given sample using only one probe.

In this study SAM-spec® is used with the ASD spectrometer but it can also be connected to other type of spectrometers such as Bruker FTNIR-Matrix.

5 Acknowledgments

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6 Reference

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