# Abstract
# Near infrared spectroscopy as a multitasking technique in the pharmaceutical field

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## Introduction

Near infrared (NIR) spectroscopy is a powerful tool in several pharmaceutical areas such as research and development (R&D), scale-up operations, and quality control of intermediary and final products. NIR spectroscopy is a multitasking technique. It can be used, for example, to predict physical and chemical properties of a sample simultaneously, or to determine when a specific process has ended. For product development and scale-up operations the physical properties of the samples are of critical importance. Furthermore, physical properties are often strongly dependent on the drug formulation. These two aspects, physical properties and chemical composition, are interconnected and must be optimised to obtain the final product. An example is given of how NIR can be used simultaneously to predict chemical composition and physical properties in a scale-up operation. The focus is on the ongoing work regarding particle size determination, but examples on the performed and future work will also be given.

## Materials and methods

Two sets of pilot-scale blended powder samples, based on paracetamol as the API, were produced, one for calibration (29) and other for validation (14). The NIR spectra was recorded in a FT-NIR instrument equipped with a diffuse reflectance probe with a 2 $cm^{-1}$ resolution, an average of 64 scans over a wave-number range between 4,250 and 10,000 $cm^{-1}$ were taken. The powders were measured by inserting the probe into the sample directly. To establish the particle size of the samples a sieving method was used. The samples were passed through a series of sieves of variable sieve opening sizes. In the end the fraction of powder retained on each sieved was weighed.

**Table 1.** Parameters for the PLS2 calibration and validation samples.

| Samples | PLS factors | *RMSE* (%) | Correlation coefficient (*R*) |
|---|---|---|---|
| Calibration | 11 | 2.1[a] | 0.999 |
| Cross validation | | 12.7[b] | 0.993 |
| Validation | | 16.6[c] | 0.988 |

[a]*RMSEC*: root mean square error of calibration, [b]*RMSECV* root mean square error of cross-validation, [c]*RMSEP:* root mean square error of prediction.

Partial least squares option 2 (PLS2) with leave-one-out cross-validation was used to correlate the NIR spectra of the 29 calibration samples with the sample size distribution. Savitzky–Golay first derivative with a filter width of 5 points was used as pre-processing method for the spectra. The calibration model was validated by determining the size distribution of 14 test samples.

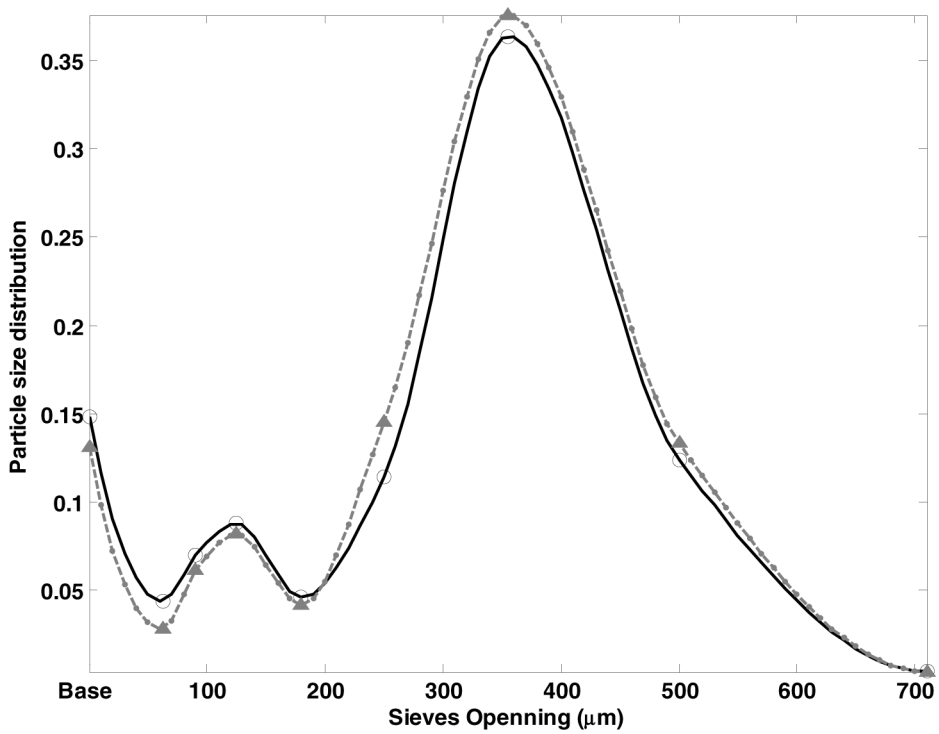


**Figure 1.** Example of the particle size distribution for the calibration set. Reference data (○), Predicted data (▲).

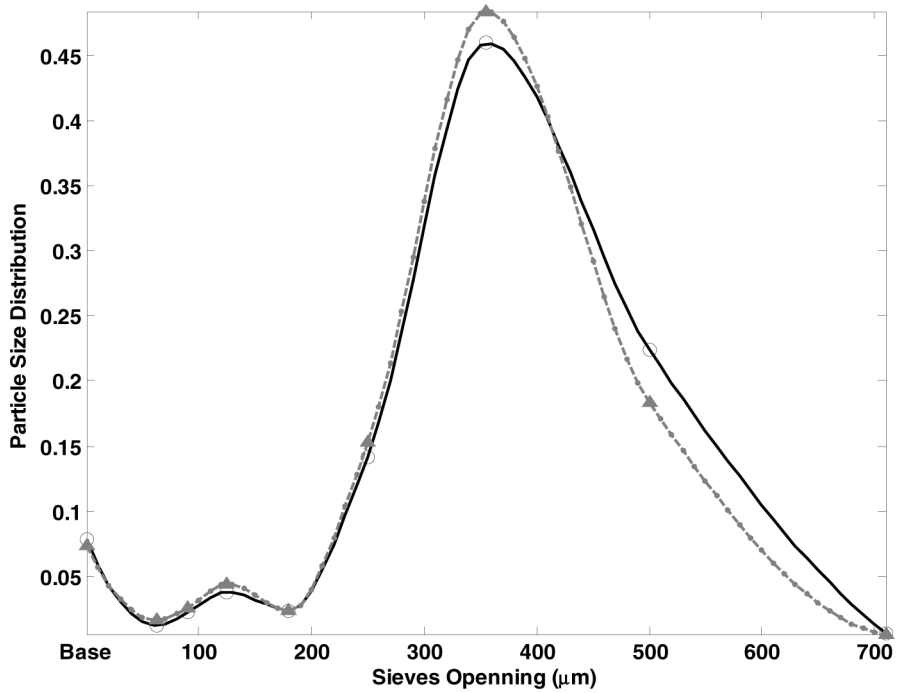


**Figure 2.** Example of the particle size distribution for the validation set. Reference data (○), Predicted data (▲).

## Results and discussion

Results showed that the prediction curve based on the NIR spectra was almost identical to the reference data curve (sieving) with a correlation coefficient ($R$) of 0.999 (Table 1 and Figure 1).

The validation results confirmed that the model can be used to predict the particle size distribution of new samples with the same chemical morphology ($R = 0.988$, see also Table 1 and Figure 2).

These samples were not constructed with the determination of particle size in mind, so no special attention was given to this subject. Nevertheless the results showed that NIR spectroscopy can be a practical tool to perform various studies with different aims, using the same set of samples.