Moisture content determination of pharmaceutical pellets by near-infrared spectroscopy: model selection, evaluation and validation.

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1 Introduction and theory.

Near infrared (NIR) spectroscopy belongs to vibrationnal spectroscopy. It offers many advantages such as no sample preparation, no sample destruction, fast data acquisition and the use of optical fibers allows "at-line", "online" and "inline" analyses. Moreover, NIR spectra contain both physical (e.g. granulometry, particle shape, polymorphism,...) and chemical information (e.g. the active pharmaceutical ingredient, moisture,...). However, each technique has its drawbacks: the NIR system must be calibrated. Indeed, calibration is a time consuming phase because the model creation takes into account the use of a reference method. Moreover, because of the great quantity of physical and chemical information found in the NIR spectra, visual spectra interpretation is difficult. Indeed, only a small piece of information is relevant for the objective investigated. Therefore chemometrical tools are used to extract the significant information arising from the physical and chemical data [1]. Two widely used chemometrical tools for spectral analyses are mathematical pre-treatments and regression methods. The first consists in suppressing the biggest part of the information that is not directly linked to the chemical nature of the sample. Examples of mathematical pretreatments include Savitzky-Golay smoothing filter, Standard Normale Variate (SNV) and Multiplicative Scatter Correction (MSC). The second links a spectrum to a concentration allowing the creation of a mathematical model. Examples of regression methods include Multi Linear Regression (MLR), Partial Least Squares (PLS) regression and Artificial Neuronal Network (ANN).

In the pharmaceutical field, the conformity analyses realized between batch production and batch release can be time consuming if all of them are performed after the manufacturing process. From this statement is born the concept of Process Analytical Technology (PAT) [2]. Indeed, PAT enables to monitor in real time each critical step of the fabrication reducing the batch release time. PAT gives also the opportunity to tune manufacturing parameters, and thus it allows to avoid the loss of potential batches. Regarding its non invasive, non destructive and fast data acquisition character, NIR spectroscopy is more and more associated with the concept of PAT.

Pellets preparation is a complex process which is divided into different operations such as blending, granulation, extrusion, spheronization and drying. The PAT approach is particularly indicated to control such a complex process. Moisture determinations to control the drying phase of the granulation process are often performed with time consuming and sample destructive techniques such as thermo-gravimetric or Karl-Fisher methods. Those techniques could be replaced by NIR spectroscopy. The NIR spectrum of water contains two major absorption bands at 5155 cm^{-1} and 6895 cm^{-1} making this technique very sensitive to the moisture content. Indeed, NIR spectroscopy has already been used in different fields such as the pharmaceutical, the food and the fuel industry to determine moisture content.

After the development of an analytical method, it is crucial to validate it in order to guarantee that the laboratory will obtain accurate results in routine analysis. The accuracy profile is used to make easier the analytical interpretation and all the useful required statistics, such as trueness, precision, quantitative limits, risk, linearity, are integrated. In addition, the accuracy profile, using β-expectation tolerance interval, makes possible a visual representation of the future performances of the analytical method [3-5].

The aim of the present study was first to develop a robust near infrared model able to determine the moisture content of pharmaceutical pellets and then to validate it for a moisture content ranging from 1 to 8 % by use of the accuracy profile.

2 Material and methods

2.1 Material

Pharmaceutical pellets with Active Pharmaceutical Ingredients x (API) were obtained from Galéphar M/F (Marche en Famenne, Belgium).

Pharmaceutical pellets were analysed by reflexion mode with a multipurpose analyser (MPA®) Fourier transform near infrared spectrometer (Bruker Optics, Brussels, Belgium) equipped with a semi-conductor room temperature sulfide lead (RT-PbS) detector. The spectra were collected with the Opus software 6.5 (Bruker Optics, Brussels, Belgium). Each spectrum was the average of 32 scans and the resolution was 8 cm^{-1} over the range from 12,500 to 3600 cm^{-1}.

A thermo-gravimetric balance (Mettler Toledo, Zaventem, Belgium) was used as reference method. Pellets samples of approximately 2 g were heated at a 105°C desiccation temperature that remained constant during the analysis. The measurement is stopped as soon as the mean weight loss per 90 seconds is lower than 1 mg. The precision of the thermo-gravimetric balance precision is ± 0.1%.

2.2 Methods

An experimental protocol was created in order to obtain a robust model using independent batches of pharmaceutical pellets for the calibration and validation steps. Moreover, this protocol was designed for 2 operators to simulate the routine conditions. The pellets were placed in a cold room to reach the targeted moisture level. The samples were first measured by FT-NIR equipment and then the reference values were determined by the thermo-gravimetric method.

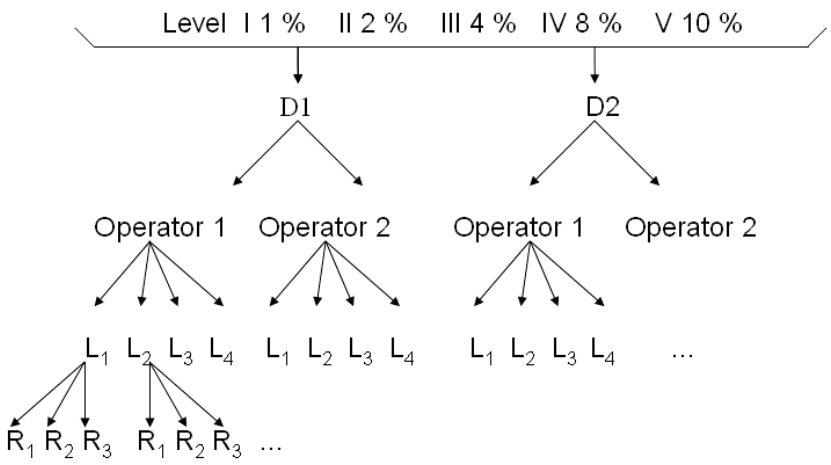

Figure 1 - Schematic illustration of the calibration protocol. D means day. L_1, L_2, L_3, L_4 represent independent batches and R_1, R_2, R_3 represent different NIR measurements of the same sample.

Prediction models based on PLS regression were carried out using the following protocol of calibration (see Figure 1). According to the spectral range and data treatment selected, a great quantity of models was obtained and conventional criteria such as R^2, SEC and bias were used to suppress model candidates with the less potential.

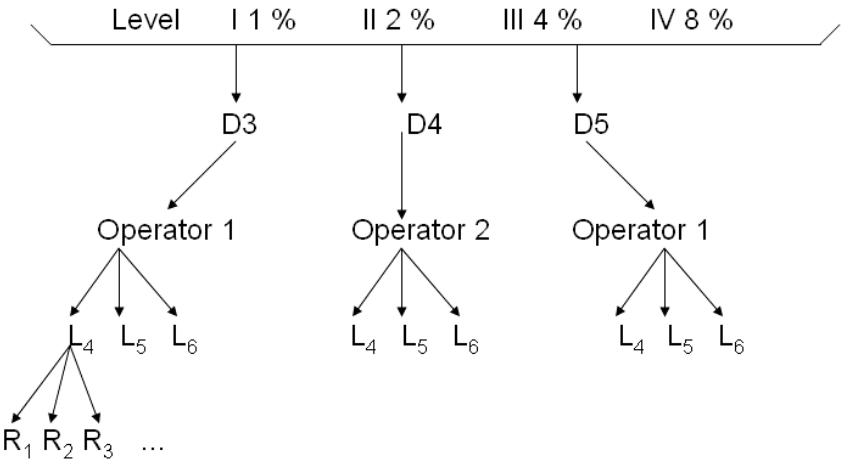

Figure 2 - Schematic illustration of the validation protocol. D means day. L_4, L_5, L_6 represent independent batches and R_1, R_2, R_3 represent different NIR measurements of the same sample.

A protocol of validation was created (Figure 2). Once the validation data were obtained, we challenged the selected potential models using accuracy profiles. The acceptance limits and the risk were set at ± 20 % and 5 %, respectively, allowing to guarantee the conformity of the pharmaceutical product.

3 Results and discussion

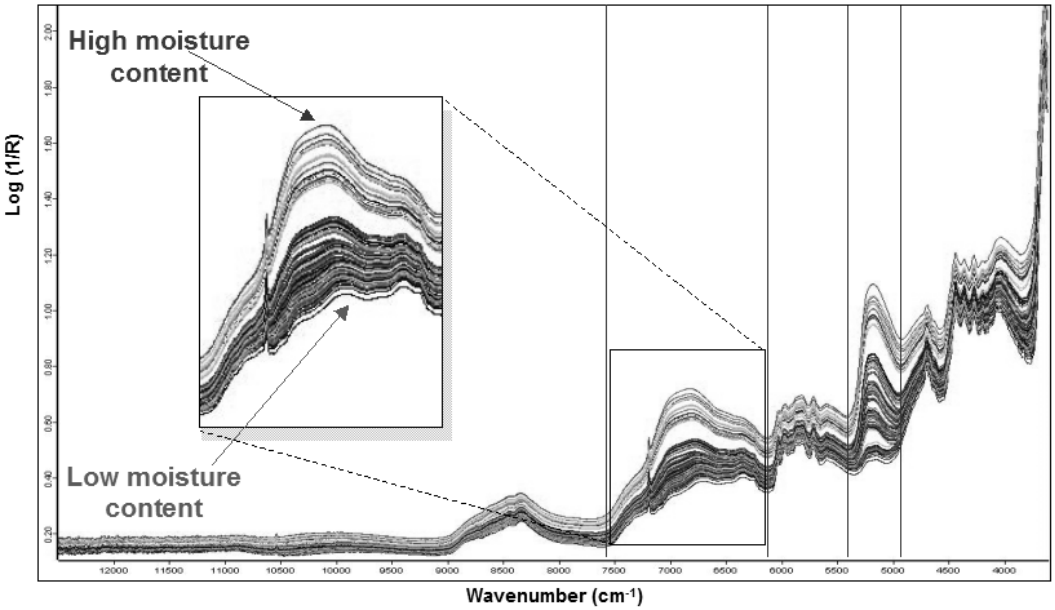

Figure 3 - Spectra of pharmaceutical pellets of one calibration series.

Two regions (7533-6136,7 cm^{-1}; 5376,9-4914 cm^{-1}) were selected taking into account the water content sensitive character (Figure 3).

Pre-treatment	R^2	SEC (%)	Bias (%)
SNV	0.9982	0.130	2.63 E-14
SG2	0.9985	0.121	6.29 E-16
SG1	0.9987	0.111	3.68 E-16
SG0	0.9986	0.117	-5.12 E-14
None	0.9986	0.116	9.62 E-11

Table 1- Conventional criteria of models using different spectral pre-treatments: Standard Normal Variate (SNV), Savitzky-Golay smoothing filter with second derivative (SG2), with first derivative (SG1), with no derivative operation (SG0) and no pre-treatment (None).

As can be seen in Table 1, it is very difficult to select the most accurate model according to these criteria. Consequently, this model selection was carried out using a different approach based on the accuracy profile.

Regarding tested models, the model without data pretreatment (see Figure 4) showed the best accuracy. Indeed, its β-expectation tolerance limits fall within the acceptance limits providing a LOQ_{inf} of 1% and a LOQ_{sup} of 8,2 %. Moreover, the bias is stable and tends towards zero all over the investigated levels.

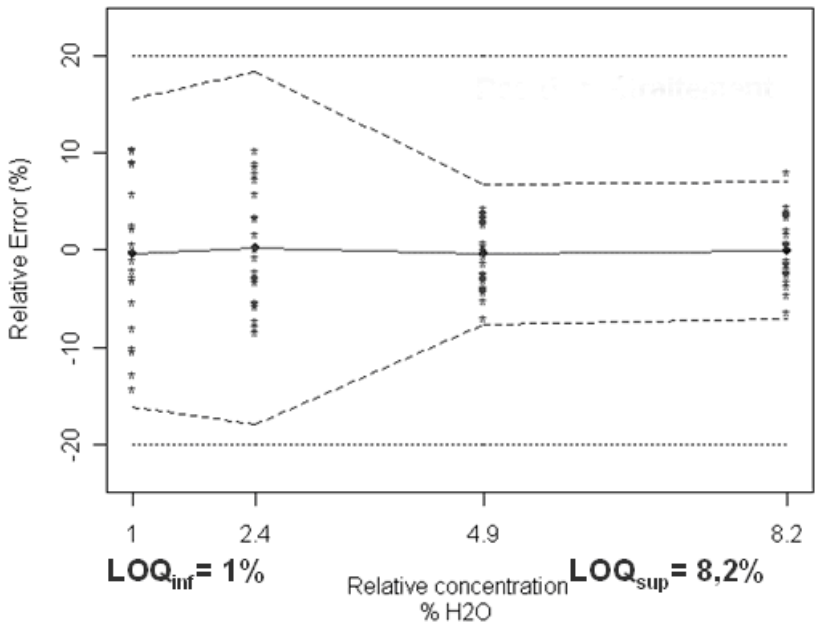

Figure 4 - Accuracy profile using raw validation data, the plain line is the relative bias, the dashed curves are the β-expectation tolerance limits (β = 95 %) and the dotted lines represent the acceptance limits (± 20 %).

4 Conclusion

This study has demonstrated that near infrared spectroscopy can be used as a non invasive, non destructive method to quantify pharmaceutical pellets moisture content. The conventional criteria were used to select some potential models but further interpretation to select the most accurate model was difficult. Therefore, another approach was used, making easier analytical interpretation while keeping all useful statistics. The use of the accuracy profile allowed us to select the most accurate model. A model that guarantees a moisture content prediction ranging from 1 % to 8 % with a defined and very acceptable precision, trueness and accuracy.

5 References

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