Active content determination of non-coated pharmaceutical pellets by near infrared spectroscopy: method development, validation and reliability evaluation.

J. Mantanus[1], E. Ziemons[1], P. Lebrun[1], E. Rozet[1], R. Klinkenberg[2], B. Streel[2], B. Evrard[3], P. Hubert[1]

[1]Laboratory of Analytical Chemistry, CIRM, University of Liège, Belgium.

[2]Galephar Research Center M/F, Belgium.

[3]Laboratory of Pharmaceutical Technology, CIRM, University of Liège, Belgium.

Purpose.

The aim of the present study was first to develop a robust near infrared (NIR) method able to determine the active content of non-coated pharmaceutical pellets. The second aim was to fully validate the method for an active content ranging from 80 to 120 % of the targeted active content. The final aim was to test the reliability of the newly developed near infrared method.

Methods.

Design: To meet the requirements of routine analysis, the calibration and validation sets were designed to include batches, operators, days and temperature conditions as sources of variability.

Data treatment: PLS regression on the calibration set was carried out for the establishment of prediction models of which ability to quantify accurately was tested with the validation set.

Results.

Conventional criteria such as the R^2, the Root Mean Square Error of Calibration and Prediction (RMSEC and RMSEP) were checked to achieve a preliminary selection of 3 models. However those criteria failed to find the most fitted for purpose method. Consequently, accuracy profiles based on tolerance intervals were performed with the validation results to assess the models predictive ability. Following this novel approach, the prediction model using signal pre-treatment Multiplicative Scatter Correction (MSC) was chosen as it showed the best ability to quantify accurately the active content over the 80-120 % active content range. Further, the reliability of the NIR method was successfully tested with new pilot batches of non-coated pharmaceutical pellets containing 90 and 110 % of the labeled active content, with blends of validation batches and Industrial batches.

Conclusion.

A NIR method able to determine the active content of non-coated pharmaceutical pellets was successfully developed and validated.

Facing the limit of interpretation of the classical and common-used criteria, the use of the accuracy profile as a decision tool has allowed to choose the best model in full accordance with the very final goal of the NIR method: to quantify accurately the active content (acceptance limits: ± 5%).

The adequacy of the NIR method and its interchangeability with its HPLC reference method was confirmed by mean of Industrial batches.