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Development of a comprehensive near infrared spectroscopy calibration model for rapid measurements of moisture content in multiple pharmaceutical products

Dipak Mainali [a], Jane Li [b,*], Peter Yehl [b], Nicholas Chetwyn [b]

[a] Department of Chemistry, Iowa State University, 1605 Gilman Hall, Ames, IA 50011, United States of America
[b] Small Molecules Analytical Chemistry and Quality Control, Genentech, 1 DNA Way, South San Francisco, CA 94080, United States of America

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ABSTRACT

Near infrared (NIR) spectroscopy has been widely used for the determination of water content in a wide variety of samples. With few exceptions, all methods employ a calibration model developed and applicable for a single product. The current study describes a NIR method using a single, comprehensive calibration model to predict the water content in tablets containing different active pharmaceutical ingredients (API). The calibration model was developed for water content range of 2–13% (w/w) using tablets containing three different APIs and different formulation compositions. To develop a robust comprehensive model, individual calibration models were sequentially developed starting from a simple model for one product to including tablets from all three projects in the final model using partial least square analysis method. Data pretreatments and spectral region selections were performed during the method development to optimize the number of factors and the correlation coefficients for cross-validation and prediction by the comprehensive model. The model reliably predicted the water content in tablet samples of these three products, and can be updated for water measurements of new drug products by adding to the model two samples of the new product for calibration purpose.

1. Introduction

Near infrared spectroscopy as an analytical tool has been widely used in pharmaceutical analysis for many years [1–9]. Over the last decade or so, pharmaceutical companies have been progressively adopting the Quality-by-Design principles expected by regulatory agencies [10] and implementing Process Analytical Technologies (PAT) to achieve full understanding of manufacturing processes and quality attributes of products [11–13]. NIR spectroscopy, capable of holistic and non-destructive sample analysis, has proven to be an invaluable PAT tool with distinctive advantages of little sample preparation, fast data acquisition, and flexibility with probes for at-line, on-line or in-line applications [12,14–16]. Typical applications include timely monitoring of critical quality attributes (CQA) of drug products such as moisture content, blend and content uniformity and coating thickness [7,17–21].

Water can affect the shelf life, physical and chemical stability and overall quality of pharmaceutical products [22–24]. The traditional wet chemistry method such as Karl Fischer titration for water content measurement is time-consuming, laborious and sample destructive. KF titration can be costly due to the use of organic solvents and treatment of chemical waste generated from the solvents use and destroyed samples. NIR spectroscopy, with its intrinsic advantages, is well suited for water determination because water shows strong absorption bands in NIR region that can provide the sensitivity and reproducibility needed for accurate measurements. Depending on the chemical and physical environment of the water molecule, the two most prominent absorption bands for water are the first overtone band of OH stretching at around 6800–7100 cm^{-1} (1470–1408 nm) and the combination band of OH stretching and bending at around 5100–5300 cm^{-1} (1960–1887 nm) [19,22,25]. Numerous reported NIR methods for water analysis clearly demonstrated the wide applicability of this technique to materials from small molecule APIs and drug products to biologics [9,20,22,26–29].

Quantitative water analysis by NIR spectroscopy is achieved through multivariate calibration methods to extract relevant chemical information from complex spectroscopic data and build calibration models for quantitation. Because the validity of a calibration model could be jeopardized by changes in instruments or

* Corresponding author. Tel.: +1 650 225 7466; fax: +1 650 467 2179.
E-mail address: li.jane@gene.com (J. Li).

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sample composition and matrix [30], most of NIR water methods employ one calibration model for each relatively well-defined type of product or process to ensure the method accuracy. A unique example of universal quantitative models for determination of moisture content in beta-lactam powder injections by NIR was reported for feasibility and limits of the models and model extensions when applied for samples of same INN (International Nonproprietary Name) from diverse formulations and sources [31]. This demonstrated that universal models can be developed to accommodate physical and chemical variations of the products, however, they quickly became very complicated with the increase of multiplicity of spectral variations. In addition, this example only utilized samples containing the same active ingredient.

For the present study, a comprehensive model for water analysis in compressed tablets was built with a set of standards that encompass significant variations in compositions and can reliably predict the water content in tablets differing in shape, size and containing different excipients and APIs. Performance between the individual and the comprehensive models was compared based on root mean square error of calibration (RMSEC), root mean square error of cross-validation (RMSECV), root mean square error of predication (RMSEP) and relative square errors of calibration and predication (RSEC and RSEP). No significant deterioration in the performance of the model was observed even as more products were included, although the minimal number of factors did increase as expected due to the increased complexity of the models. This method can be expanded for new products by updating the model with only two samples of the new products, and offers a fast and effective way to determine the moisture content in tablets to support product development.

2. Materials and methods

2.1. Materials

Uncoated tablets produced in house at Genentech (South San Francisco, CA, USA) with three different proprietary Genentech APIs were used for the study. API I and API III are both highly hygroscopic. Tablets containing API I were exposed to different humidity levels at ambient temperature to generate the reference samples with moisture level between 2% and 13% (w/w) for building NIR calibration method. The main excipient in all the tablets is microcrystalline cellulose (Avicel PH101, 102 or 103) purchased from FMC Biopolymer (Philadelphia, PA, USA). Tablets of API II also contained lactose monohydrate (Foremost Farms USA, Baraboo, WI, USA) at the amount similar to MCC. All tablets were manufactured using roller compaction process under different process conditions that were optimized for each product through Design of Experiments (DOE).

2.2. FT-NIR instrument and data acquisition

NIR spectra of the tablets were acquired with an Antaris II Fourier-Transform Near Infrared (FT-NIR) analyzer from Thermo Scientific (Madison, WI) equipped with Integrating Sphere and an Indium Gallium Arsenide (InGaAs) detector in diffuse reflectance mode. Thermo Scientific OMNIC software version 8.3 accompanying the instrument was used for the collection of all spectra. One spectrum was collected for each face of the round, oval or oblong shaped tablet. Each spectrum was the average of 16 scans in the range of 10,000 cm^{-1} to 4000 cm^{-1} with 8 cm^{-1} resolution. For each tablet, spectra from the two faces were averaged as one for calibration or quantitation.

Table 1
Reference Samples with moisture content in the range of 2–13% (w/w).

API	Sample	Tablet	Water by KF (%, w/w)
I	1	Round	2.77
	2	Round	3.13
	3	Round	4.41
	4	Round	5.52
	5	Round	5.60
	6	Round	6.33
	7	Round	12.37
	8	Round	12.80
	9	Oblong	3.59
	10	Oblong	3.62
	11	Oblong	5.21
	12	Oblong	5.31
	13	Oblong	5.30
	14	Oblong	6.12
	15	Oblong	6.20
	16	Oblong	6.17
	17	Oblong	7.08
	18	Oblong	6.95
	19	Oblong	10.41
	20	Oblong	8.93
II	21	Round	4.99
	22	Round	4.98
	23	Oval	5.28
III	24	Oblong	2.25
	25	Oblong	2.18

2.3. Karl Fischer

Coulometric Karl Fischer 851 Titrando (Metrohm, Switzerland) equipped with 774 oven sample processor and Tiamo 2.3 software was used as the reference method to measure water content in the tablet samples. Each tablet was weighed, ground into powder, transferred to titration vials and sealed for the KF measurements. Precaution was taken to complete the grinding, powder transfer and vial sealing within 5 min for each sample after NIR spectra collection. This was especially important for tablets of API I and III due to their high hygroscopicity, so that potential changes in water content because of the sample exposure to ambient conditions can be minimized.

2.4. NIR calibration model

In order to build the calibration models over an expanded range of moisture content, tablets containing the API I were exposed to different humidity levels at ambient temperature to generate the reference samples with moisture level between 2% and 13% (w/w). Samples of the lowest moisture content were stored with desiccant, and samples stored under ambient conditions without desiccant had moisture level of ~5% (w/w). Higher moisture levels (>5%, w/w) were obtained by exposing the tablets overnight to various high humidity conditions created by saturated salt solutions. These reference samples were analyzed by NIR and KF for moisture content. Of the thirty tablets analyzed, twenty-five were used for building NIR calibration models and five were used for validation of the models to allow the calculation of RMSEP and performance index (PI) values of the models. Table 1 summarizes the reference samples and their moisture contents by KF.

Chemometric software package TQ Analyst version 8 by Thermo Scientific (Madison, WI) was used to build the NIR calibration models. The models were built with partial least square (PLS) method by assigning KF data to the corresponding NIR spectra. Spectral pretreatments that were performed to build each calibration model included Savitzky–Golay smoothing with no, first-degree or second-degree derivative. Seven data points and third order polynomial were used for Savitzky–Golay smoothing. The