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Calibration transfer from powder mixtures to intact tablets: A new use in pharmaceutical analysis for a known tool

Leandro S.A. Pereira [a], Maíra F. Carneiro [b], Bruno G. Botelho [a,1], Marcelo M. Sena [a,c,*]

[a] Departamento de Química, ICEx, Universidade Federal de Minas Gerais, 31270-901 Belo Horizonte, MG, Brazil
[b] Fundação Ezequiel Dias (FUNED), 30510-010 Belo Horizonte, MG, Brazil
[c] Instituto Nacional de Ciência e Tecnologia em Bioanalítica, 13083-970 Campinas, SP, Brazil

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ABSTRACT

Calibration transfer is commonly used for spectra obtained in different spectrometers or other conditions. This paper proposed the use of calibration transfer between spectra recorded for the same samples in different physical forms. A new method was developed for the direct determination of nevirapine in solid pharmaceutical formulations based on diffuse reflectance near infrared spectroscopy (NIRS) and partial least squares (PLS). This method was developed with 50 powder mixtures and then, successfully extended to the quantification in intact tablets by using calibration transfer with double window piecewise direct standardization (DWPDS). This chemometric strategy provided good results with a small number of tablet transfer samples, only seven, prepared out of the narrow range of active principle ingredients (API) content around the nominal value of the formulation (100%). The method was fully validated in the working range of 83.0–113.9% of nevirapine and the use of DWPDS allowed to significantly decreasing the root mean square error of prediction (RMSEP) from 4.8% (tablets predicted by a model built with only powder samples) to 2.6%. The range of relative errors decreased from −5.1/8.7% to −4.6/3.3%. Considering that the amount of raw materials demanded for preparing tablets is up to ten times higher than for powder mixtures, this type of application is of particular interest in pharmaceutical analysis. In the context of process analytical technology (PAT), the use of the same multivariate model in different steps of the production is very advantageous, saving time and labor.

1. Introduction

The combined use of near infrared spectroscopy (NIRS) and chemometric tools of multivariate calibration has been consolidated as a viable alternative for the quality control of active ingredients in pharmaceutical formulations. NIRS provides simple, rapid, low cost and non-destructive methods, which require a minimum of sample pre-treatment and are environmentally friendly, without neither the consumption of solvents nor generation of chemical waste. In the last years, methods based on NIRS have been successfully applied for analysis in formulations of different physical forms, such as solutions, suspensions, powder mixtures and intact tablets [1–10]. Particularly stimulating for the development of NIRS methods was the Process Analytical Technology (PAT) initiative, issued by the Food and Drug Administration (FDA) [11]. It has opened perspectives for incorporating new technologies in the production and quality check of pharmaceutical products, considering the need of control of all the steps of the process, from the raw materials, going through the intermediates, to the final products.

Most formulations are available in solid forms, mainly tablets. For the production of tablets, a crucial intermediate step is the mixing of raw materials: active principle ingredients (API) and excipients. In order to analyze tablets, some analytical methods have simply added a step of pulverization and measured powder mixtures [5,10], with the drawbacks of increasing sample manipulation and analytical costs. Other methods have required the production of dozens of intact tablets with a range of chemical composition wider than the narrow API concentration interval around the nominal value. One example is a method developed based on the production of a mixed sample set including powdered samples plus tablets, in order to introduce production variability [1]. Other example is a slightly different approach, at which production tablets were ground and over or under-dosed

* Corresponding author at: Departamento de Química, ICEx, Universidade Federal de Minas Gerais, 31270-901 Belo Horizonte, MG, Brazil. Fax: +55 31 34095700.
E-mail address: marcsen@ufmg.br (M.M. Sena).
[1] Present address: Instituto de Engenharia e Tecnologia, Centro Universitário de Belo Horizonte, 30455-610 Belo Horizonte, MG, Brazil

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by adding known amounts of the formulation components [8]. However, as production samples have been used, a reference method to quantify the actual content of API must be employed. A more recent alternative, that has not demanded a reference method for the calibration samples, calculates the difference between the spectra of tablets and powder mixtures of identical composition prepared in the laboratory, generating a set of vectors that define the overall process variability [7]. In the present paper, it was proposed another alternative that also requires no reference method and uses fewer samples. The method is based on a new use for a known chemometric tool, calibration transfer.

A practical limitation to multivariate calibration occurs when an existing model is applied to spectra obtained under different instrumental, environmental or sample conditions. Even if identical samples were measured, the spectral variation of the two responses that is modeled by the method might differ [12]. If the sources of variation are known, every sample can be remeasured, demanding the reconstruction of a robust model. To avoid an expensive and time consuming full recalibration, the alternative of correcting instrumental and environmental differences by calibration transfer methods has been proposed [13]. The most common methods for correcting these differences are based on standardization of spectral responses, direct standardization (DS) and piecewise direct standardization (PDS) [12–14]. In these methods, the objective is to provide the same reading for a sample measured on a secondary (child or slave) condition as it does on the primary (parent or master) condition at which the calibration model was generated. DS directly relates spectral response matrix of samples measured in the primary condition, $\mathbf{S}_1$, to their responses obtained on the secondary one, $\mathbf{S}_2$, through a linear relationship described by the transformation matrix **F**, which is estimated according to Eq. (1),

$$\mathbf{F} = \mathbf{S}_2^{+}\mathbf{S}_1 \quad (1)$$

where $\mathbf{S}_2^{+}$ is the pseudo-inverse of $\mathbf{S}_2$.

F is typically estimated by means of PCR or PLS and subsequently used for projecting the secondary measurement space so that its property values can be predicted with the old model. A serious drawback of DS is that the number of samples is often much smaller than the number of channels involved in the regression, turning it prone to overfitting [12,14]. A way to circumvent this problem is to reduce the number of channels, which forms the basis of PDS. PDS is similar to DS, but incorporates the use of a moving window that steps across the variable range. For each wavelength of a sample spectrum, the absorbance values for the secondary condition are regressed against the corresponding values in a spectral window of neighboring wavelengths measured at the primary condition. PDS models may perform adequately where features are present in the transfer spectra, but not very well when featureless regions are frequent. Thus, a further modification has extended the PDS algorithm by incorporating a double window (DWPDS) [15]. DWPDS is based on a window data on both primary and secondary conditions used in the standardization, which increases the modeling flexibility. The form of the model is identical to PDS and some authors have considered it the best method for transferring NIRS models [16].

In the last paragraph, the emphasis in calibration transfer between samples measured at different conditions was purposefully adopted. However, most of published papers have been restricted to different instrument conditions [17–19] and a few ones have dealt with calibration transfer changing another condition, such as the temperature of measurements [20,21], or measurement time in milk analysis [22]. Considering that powdered samples present higher scattering than compressed ones [6], thus, affecting their NIR spectra, this paper proposed the calibration transfer between the same samples measured at different physical forms. In pharmaceutical analysis, this strategy is advantageous in terms of practicality, simplicity and costs reduction, since the same model can be used in different steps of the production and few samples of intact tablets outer of production specifications are required for constructing the model.

The analyte chosen for developing this methodology was nevirapine (NVP). NVP was the first nonnucleoside reverse transcriptase (RT) inhibitor used in clinical treatment of HIV disease and still being one of the most used medicines in HIV treatment, due to its robust virologic efficacy and a good safety profile [23]. In Brazil, NVP formulations are produced in governmental industries, due to its strategic importance for the public health. NVP has no quantitative reference method described in Brazilian Pharmacopeia [24], and a UV spectrophotometric method described for similar formulations is used as reference in local industry. In the literature, NVP has been determined in pharmaceutical formulations by chromatographic and electrophoretic methods, such as HPLC [25], HPTLC [26], MEKC [27] and CZE [28]. As far as it is known, NVP formulation has not been previously determined by a simple and direct NIR procedure. The NIRS method was initially developed and validated for powder mixtures and then, transferred to intact tablets by using the DWPDS method.

2. Materials and methods

2.1. Samples, design and spectra acquisition

All the chemical reagents used were of analytical grade, purchased from certified suppliers and used without further purification. The target formulation contains NVP, two major and five minor excipients. Two four-component experimental designs were built. The main design consisted of 78 samples that were prepared only as powder mixtures. The second one consisted of 9 transfer samples that were prepared as both powder mixtures and tablets. Random experimental designs were employed in order to avoid chance correlations and increase method robustness [2]. Random numbers within each component range were generated for each sample using Microsoft Excel®. The NVP content ranged from 80% to 120% of the nominal value of the target pharmaceutical formulation (200 mg of NVP per 800 mg, the average mass of one tablet) and two major excipients ranged independently from 95% to 105%. The other five minor excipients were modeled as one component design and their masses were kept constant in all samples. Due to the random values employed, the total weights of each sample were not constant and thus, the effective API contents were recalculated. The composition of all the samples of the main (1–78) and transfer (T1–T9) designs are shown in Table 1 of Supplementary materials. Due to industrial secrecy, the excipients composition is not shown.

For the main experimental design, 15 g of each powder mixture sample were produced. For the transfer design, 200 g of each sample were produced, from which 15 g were used as powder mixtures and the remaining powder was compressed as 13 mm

Table 1
Results of the optimization of PLS model through outlier detection.

Model	1st	2nd	3rd	Final[a]
Number of calibration samples	61	56	50	50
Number of LV	4	5	6	6
RMSEC (%)	4.4	1.9	1.1	1.1
RMSEP (%)	3.9	3.5	3.2	1.7

[a] The final model includes the calibration transfer and outlier detection for the validation set.