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RESEARCH ARTICLE

A Multivariate Control Chart Approach for Calibration Transfer between NIR Spectrometers for Simultaneous Determination of Rifampicin and Isoniazid in Pharmaceutical Formulation

Eduardo Wagner Vasconcelos de Andrade, Camilo de Lelis Medeiros de Morais, Fernanda Saadna Lopes da Costa and Kássio Michell Gomes de Lima*

Biological Chemistry and Chemometrics, Institute of Chemistry, Federal University of Rio Grande do Norte, Natal, Brazil

ARTICLE HISTORY

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Abstract: ***Background:*** Multivariate transfer techniques have become a widely accepted concept over the past few years, since they avoid full recalibration procedures when instruments are changed to analyze a specific sample.

Objective: This paper reports a multivariate control chart transfer approach between two near infrared (NIR) spectrometers for simultaneous determination of rifampicin and isoniazid in pharmaceutical formulation using Direct Standardization (DS).

Method: The control charts are based on the calculation of Net Analyte Signal (NAS) models and the transfer samples are selected by the Kennard-Stone (KS) algorithm. Three control charts (NAS, interference and residual) transferred on both the master and slave instruments were measured.

Results: As a result, a classification model for rifampicin and isoniazid developed on a primary instrument has been successfully transferred to a secondary instrument. The spectral differences after the standardization procedure were considerably reduced and errors values found in the charts for both analytes were comparable with the errors obtained for the original chart models.

Conclusion: The proposed approach appears to be a valid alternative to the commonly used transfer of multivariate calibration models in simultaneous determination of isoniazid and rifampicin in pharmaceutical formulation.

Keywords: Multivariate control chart, NAS, isoniazid, rifampicin, direct standardization, NIR.

1. INTRODUCTION

Multivariate calibration transfer techniques (also known as instrumental standardization) have become a widely accepted concept over the past few years mainly due to avoiding the use of time-consuming complete recalibration procedures [1-5]. Usually, the instrument standardization procedure for multivariate calibration transfer involves two steps: (i) a set of standardization samples are measured on both instruments to evaluate their different responses; (ii) standardization parameters are computed with standardization samples and used for spectra transfer [6, 7].

Direct standardization (DS) [8], Piecewise Direct Standardization (PDS) [9], Orthogonal Signal Correction (OSC) [3], Reverse Standardization (RS) [10], Piecewise Reverse Standardization (PRS) [11], slope and bias correction (SBC) [1], Orthogonal Projections to Latent Structures (O-PLS) [12] and Model Updating (MU) [4] are examples that have been successfully applied to various calibration transfer problems. These methods relatively correct differences between data collected by two instruments where the entire spectra from the new (secondary) instrument are transformed by relating its spectral variables (e.g., wavelengths) to resemble the spectral data from the original (primary) instrument used to build a prior calibration model [13].

On the other hand, there are many situations in which the simultaneous monitoring or control of two or more related quality–process characteristics is necessary. Multivariate control charts based on principal component analysis [14-16], partial least squares [17], multivariate exponential weighted moving average [18], multivariate cumulative sum [19] and Bayesian probability [20] are some examples for building an empirical model of a set of measurements achieved under Normal Operating Conditions (NOC).

An interesting approach for quality multivariate control chart is based on Net Analyte Signal (NAS) [21-24]. This method is carried out by the decomposition of a sample spectrum into a vector that is unique for the analyte; a vector re-

*Address correspondence to this author at the Biological Chemistry and Chemometrics, Institute of Chemistry, Federal University of Rio Grande do Norte, Natal 59072-970, Brazil; Tel: +55 84 3342 2323;
E-mail: kassiolima@gmail.com

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lated to the other compounds in the sample (interfering constituents); and a remaining residual vector [25]. Thereafter, the statistical limits for the NAS control charts are derived from the NAS value for each of the NOC spectra calculated [26].

This paper investigates a multivariate control chart transfer approach between two near infrared (NIR) spectrometers (primary and secondary) for simultaneous determination of rifampicin and isoniazid in pharmaceutical formulation, which are important drugs used in tuberculosis treatment [27, 28]. Three control charts (NAS, interference and residual) transfer using NAS and DS between the primary and secondary instruments were developed. These control charts were built with the spectral data before and after calibration transfer, in which the classification rates were evaluated before and after DS according to the upper and low limits on these charts.

2. MATERIALS AND METHOD

2.1. Samples

The pharmaceutical preparation studied contained isoniazid (99.29%, Amsal Quality Control Laboratory, India) and rifampicin (98.87%, Sanofi Aventis, Italy) as the active principles and four excipients (magnesium stearate, sodium starch glycolate, talc and amide). All compounds (active principles and excipients) were supplied by the Center for Food and Drug Research of the Federal University of Rio Grande do Norte (NUPLAM/UFRN) – Brazil. The capsules produced at UFRN were available in one absolute active pharmaceutical ingredient (API) content per dose. The capsules were uncoated, thus permitting diffuse reflectance.

Laboratory samples were prepared by a D-optimal experimental design using MODDE® 4.0 (MKS Data Analytics Solutions, Umeå, Sweden). D-optimal design is performed when the classical symmetrical design cannot be used because the shape of the experimental region is irregular or the number of experiments selected by a classical design is too large. A total of 120 pharmaceutical formulation samples were generated to efficiently represent the design space for the large number of possible combinations of these substances and to build the NAS charts. These samples were weighed on an analytical scale with a total weight accuracy of 0.012 g. Then, the samples were mixed for 3 min and vortexed for 1 min before NIR analysis.

Next, the samples were used to design news samples varying API concentrations (isoniazid and rifampicin) and to provide a variable matrix from which NAS charts could be derived providing an independent set of samples that could be used to check the accuracy of the control charts for each instrument. Samples containing only the excipients (blank samples) were also prepared. The samples (blank, in control and out-of-control) used for NAS, interference and residual charts were distributed as follows:

i) 20 blank samples: 10 samples for isoniazid and 10 samples for rifampicin;

ii) 10 samples in control (isoniazid, rifampicin, magnesium stearate, microcrystalline cellulose, talc and starch);

iii) 20 samples in control (2.5% of the nominal content of each active substance);

iv) 20 samples in control (5.0% of the nominal content of each active substance);

v) 20 samples out-of-control (8.0% of the nominal content of each active substance);

vi) 20 samples out-of-control (12.0% of the nominal content of each active substance);

vii) 10 samples out-of-control (16.0% of the nominal content of each active substance).

2.2. Instruments

The primary (master) instrument used was an Antaris MX Fourier Transform NIR spectrophotometer (Thermo Fisher Scientific Inc., USA) equipped with a transflectance optical fiber probe being positioned onto the sample surface (less than 1 cm and at 90° from the surface). The transflectance probe was washed with ethanol (70% v/v) and dried using tissue paper after each sample. The spectrum of a polytetrafluoroethylene sample was used as the background. The NIR spectra were obtained over a range of 1000–2400 nm, and were recorded with a spectral resolution of 1 nm, with 32 scans co-added. The measurement time was 26 s (32 scans) per spectrum. A Fourier Transform NIR MPA spectrometer was used as the secondary (slave) instrument (Bruker Optics, Germany) equipped with an integrating sphere *via* diffuse reflection mode. Each measured spectrum (in triplicate) was the average of 32 scans obtained with a resolution of 2 nm and over the range of 1000–2400 nm. The background spectrum was recorded using a gold coated slide. Spectral measurements for both instruments were done in an acclimatized room under controlled temperature of 22°C and 60% relative air humidity.

2.3. Data Analysis

The data import, pre-processing, and construction of multivariate control charts were implemented in MATLAB® version 7.12.0 (MathWorks Inc., USA) using an in-house developed algorithm. Different preprocessing methods were tested, including baseline correction; Multiplicative Scatter Correction (MSC); variance scaling; derivative; and Savitzky-Golay smoothing using first- and second-order polynomial functions varying the number of window points (7, 11 and 15). However, the best pre-processing were baseline correction and MSC for isoniazid charts; and baseline correction for rifampicin charts. These pre-processing were the same for both equipment. The technique chosen for selection of transfer samples was the classic Kennard Stone (KS) algorithm [29].

3. THEORY

Fundamentally, in order to build a multivariate control chart based on NAS, an out-of-control indicator is required for diagnostic and corrective measures. In this sense, two steps are required: 1) (diagnostic) discovery which measurement variables contribute to the out-of-control signal and 2) (corrective) determining what occurs in the process that disturbs the behavior of these variables.

The first step to perform before any standardization method is to select the standardization samples to transfer, which is commonly obtained by using sample selection techniques, such as KS algorithm [29] or leverage [9]. The number of transfer samples is evaluated by an arbitrary cost function, which for calibration models is usually the root-mean-squared error of prediction [13]. In our case, for classification purpose, this cost function was calculated as the classification rate of the NAS control charts.

The DS is a multivariate standardization method employed to correct relatively large differences between data collected by two instruments [9]. In this method, the entire spectra from the new (secondary) instrument are transformed by relating its spectral variables (*e.g.*, wavelengths) to resemble the spectral data from the original (primary) instrument used to build a prior calibration model [13]. The linear relationship between the primary and secondary response is described by the transformation matrix F according to Eq. (01) [4]:

$$S_1 = S_2F \quad (01)$$

where S_1 and S_1 are the data matrices of the standardization samples for the primary and secondary instruments, respectively.

Thus, the transformation matrix is estimated in a least-squares sense according to Eq. (02) [30]:

$$F = S_2^+ S_1 \quad (02)$$

where S_2^+ is the pseudo-inverse of S_2. S_2 must contain independent rows (samples) or columns (variables) for the pseudo-inverse calculation to be feasible (Eq. (03)):

$$S_2^+ = (S^TS)^{-1}S^T \quad (03)$$

After the calculation of F, the projection of the response vector for a new sample x from the secondary instrument on the original space from the primary instrument is estimated according to Eq. (04) [4]:

$$\hat{X}^T = X^TF \quad (04)$$

where $\hat{x}$ is the standardized response vector for x.

In order to solve possible problems related to different background information in both instruments, the standardization process was performed using the background correction method [30] where the data matrices of standardization samples from the primary and secondary instruments relate to each other by the transformation matrix calculated with the background correction F_b and an additive background correction vector b_s according to Eq. (05):

$$S_1 = S_2F_b + 1b_s^T \quad (05)$$

where b_s is obtained using Eq. (06):

$$b_s = s_{1m} - F_b^Ts_{2m} \quad (06)$$

in which S_{1m} is the mean vector of matrix S_1 and S_{2m} is the mean vector of matrix S_2.

Multivariate control charts based on NAS provide multivariate product quality monitoring and they are carried out in two stages: (i) model building and (ii) calculation of statistical limits [26]. The first stage consists on the decomposition of a sample spectrum r into three vectors: a vector r_{NAS} that is unique for the analyte; a vector r_{INT} that is related to the other compounds in the sample (interfering constituents); and a residual vector r_{res} [25]:

$$r = r_{NAS} + r_{INT} + r_{res} \quad (07)$$

In the second stage, the statistical limits of the NAS control charts are derived from the NAS value for each of the NOC spectra calculated as follows:

$$nas_{NOC} = R_{NOC}^Tb_k \quad (08)$$

where nas_{NOC} is a vector with the NAS value of the individual NOC spectra; R_{NOC} is the set of NOC spectra used to set the control limits for the NAS chart; and b_k is the orthogonal part of the model spectra used to define the NAS direction on the interference space [26]. The NAS values are assumed to follow a normal distribution, which can be verified by statistical normality tests such as QQ plot [31]. Its mean and standard deviation are computed for statistical limits (95% confidence limits called the upper and lower warning lines, and 99.7% confidence limits called the upper and lower action lines) that are plotted in the NAS control chart [26]. The classification rate was calculated based on the 2-sigma (95%) confidence interval; so that any sample outside this limit would be considered out of control. The 3-sigma (99.7%) confidence interval was not used for classification evaluation but it represents the limit with the largest probability for a sample be identified as out of control.

The interference chart is based on projecting the RNOC matrix on the interference space. The projected "under control" spectra occupy a restricted region on the interference space, wherein the pharmaceutical formulation is constructed with placebo and blank samples. The validation of these control charts is made by using "in-control" and "out-of-control" samples, based on the concentration of the active pharmaceutical ingredient [25, 26]. The residual charts are obtained after calculation of NAS and interference vector, in which its control limits are estimated based on Q-statistics by fitting a chi-squared distribution to the reference distribution obtained from NOC data [25, 26]. The Q-statistics is the first type of statistical calculation recommend to test significance of an individual observation vector [32]. It is calculated for a sample vector following a chi-squared distribution [26]:

$$Q_{NOC} \sim gx_h^2 \quad (09)$$

where Q_{NOC} contains the Q-statistics of the NOC spectra; g represents the weight to account for the magnitude; and X_h^2 is the chi-squared distribution to the reference distribution obtained from NOC data, where the parameter *h* denotes the degrees of freedom. Using this statistics, if we have a situation where the residual vector of a new sample is not only random noise then the observation will have a large Q-statistics and flag in the residual chart [26]. In addition, the chi-squared distribution is very adequate for large samples sets [33], therefore, being very suitable for industrial or routine applications. On the other hand, statistics such as F dis-

tribution was not used due to the lack of sensitivity to detect normality of distribution in the residuals [33].

The control chart transfer procedure is summarized on the flowchart in Fig. (**1**). In this, the spectral data is separated into three sets: Xcal(M) corresponding to the calibration samples of the primary (master) instrument; Xcal(S) corresponding to the calibration samples of the secondary (slave) instrument; and Xpred(S) corresponding to the prediction samples of the secondary instrument to be analyzed using the control chart of the primary instrument. The spectral resolution and the number of calibration samples used for transferring data from both instruments must be equal or otherwise all algebraic operations will not be possible since the matrices sizes would be different. Therefore, an algorithm for correct spectral resolution was inserted on the transfer approach. This algorithm resizes the spectra of higher resolution to match with the spectra of lower resolution keeping its shape constant; in other words, it "compresses" the largest spectra. The transfer samples are selected by the calibration indexes found employing KS algorithm on the Xcal(M) data.

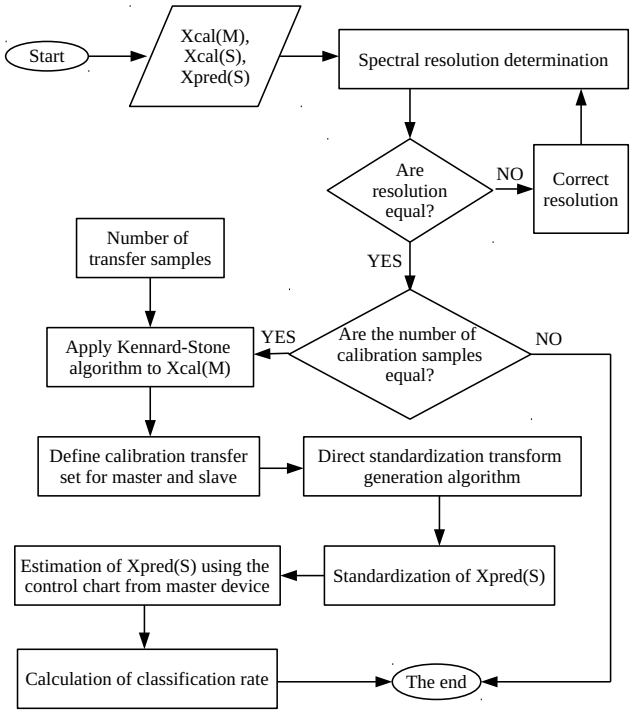

Fig. (1). Flowchart for control chart transfer procedure using DS.

The DS transferring is performed by combining the transfer samples from both instruments. Then, the prediction set from the secondary instrument (Xpred(S)) is standardized by using the transformation matrix with additive background correction (Eq. (05)). At the end, the standardized Xpred(S) is analyzed by the NAS-based primary control charts and the classification rate is calculated. This parameter is used as the cost function to define the ideal number of transfer samples. After the model is optimized with the ideal number of samples to transfer, all external prediction samples from the secondary instrument are standardized and predicted using the primary control chart.

4. RESULTS AND DISCUSSIONS

Fig. (**2**) shows the raw NIR spectra of a pharmaceutical formulation sample acquired on the two instruments employed in this study. They are the averages of triplicate measurements for each sample recorded in the region from 1000 to 2400 nm.

As mentioned before, the primary and secondary instruments were from different manufacturers and different measurement procedures were employed with each. As can be seen in Fig. (**2**), there are resulting spectral differences between master and slave measurements. Some preprocessing methods needed to be applied to reduce instrumental noise and light scattering that can affect the baseline. The performance of each preprocessing method was evaluated according to their correct classification rate (predicted sample index equal to the correct class index) and incorrect classification rate (predicted sample index different from the correct class index) using a calibration and validation set. The best prediction rates were obtained using baseline correction combined with MSC for isoniazid control chart; and baseline correction for rifampicin control chart (Fig. **3**). The spectral differences between both instruments motivate the use of control chart transfer techniques.

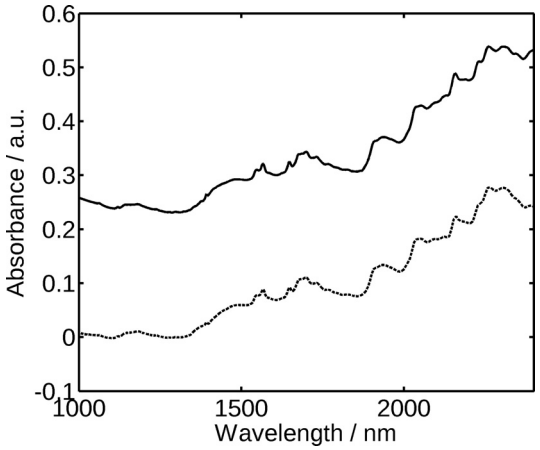

Fig. (2). Spectra of a representative pharmaceutical formulation sample acquired on two NIR instruments: dashed line represents the NIR spectrophotometer equipped with transflectance optical fiber probe (primary); and the continuous line represents the NIR spectrophotometer equipped with an integrating sphere (secondary).

For isoniazid, the control charts (NAS, interference and residual) constructed for master instrument achieved the following correct classification rates: 92% (NAS chart); 100% (interference chart); and 100% (residual chart). When the isoniazid model was directly applied to the slave instrument, the following correct classification rates were achieved: 71% (NAS chart); 100% (interference chart); and 100% (residual chart). The prediction accuracy was particularly poor for the slave instrument because of the major spectral differences between this instrument and the master. Fig. (**4**) and Fig. (**5**) show the control charts developed for isoniazid using the master and slave instrument, respectively. These results justify the application of multivariate control chart transfer to the acquired data, as without a transfer technique, the correct classification rate may be completely different when the NIR spectra from an instrument is validated into another.

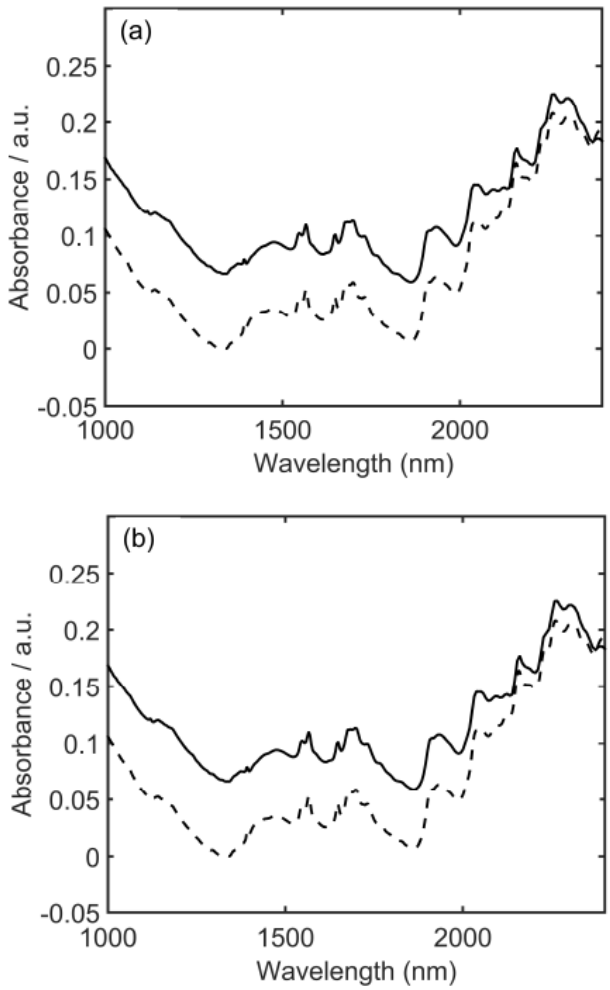

Fig. (3). NIR spectra after application of: **a**) baseline to rifampicin; **b**) baseline and MSC to isoniazid. Dashed line – primary instrument; and continuous line – secondary instrument.

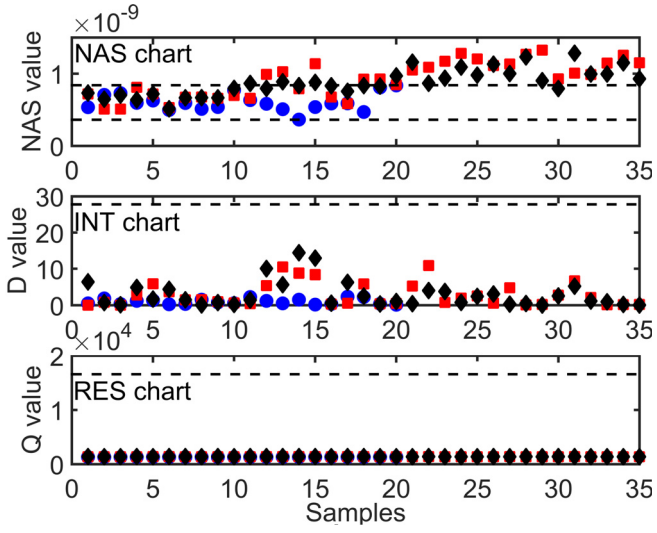

Fig. (4). Control charts for isoniazid using master instrument: (●) calibration, (■) validation and (◆) prediction. NAS: Net Analyte Signal; INT: Interference; RES: Residual.

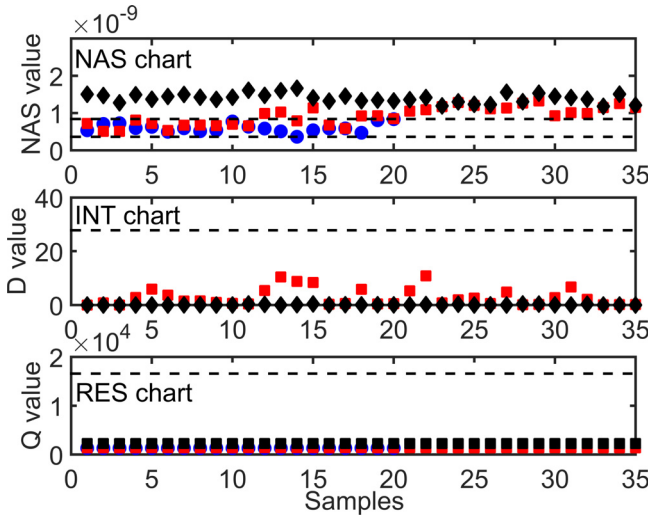

Fig. (5). Control charts for isoniazid using slave instrument: (●) calibration, (■) validation and (◆) prediction. NAS: Net Analyte Signal; INT: Interference; RES: Residual.

The prediction performance of the multivariate control charts (NAS, interference and residual) for isoniazid in the master and slave instruments after DS multivariate control chart transfer procedure were calculated by using 20 transfer samples selected by KS algorithm. The standardization improved the correct classification for NAS chart from 71% (without DS) to 92% (after DS); and maintained the same correct classification rates for interference (100%) and residual (100%) charts. These correct classification rates are satisfactory, mainly for NAS chart, considering the simplicity of the multivariate control chart transfer used, and showing their importance to avoid a full recalibration step.

For rifampicin, the control charts (NAS, interference and residual) built for the master instrument achieved the following correct classification rates: 86% (NAS chart); 99% (interference chart); and 73% (residual chart). When the isoniazid model was directly applied to the slave instrument, the following correct classification rates were achieved: 71% (NAS chart); 99% (interference chart); and 60% (residual chart). The prediction accuracy was particularly poor for the slave instrument because of the major spectral differences between this instrument and the master. However, the standardization improved the correct classifications for NAS chart (86%), interference chart (99%) and residual chart (73%) using 11 transfer samples selected by KS algorithm. Fig. (**6**) and Fig. (**7**) show the control charts developed for rifampicin using the master and slave instruments, respectively.

These classification values demonstrate that after multivariate transfer the response obtained with the secondary instrument gave the same results observed with the primary instrument despite the differences of resolution, equipment and probe. Therefore, the standardization methodology shown herein was a successful case for rinfampicin and isoniazid determination using NAS control charts constructed with different NIR spectrometers, which can avoid a full recalibration when analyzing these samples with different NIR equipment and shows its potential to further applications.

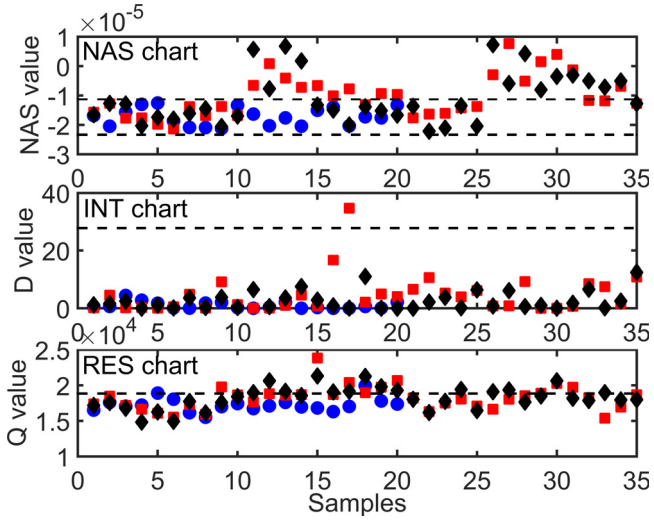

Fig. (6). Control charts for rifampicin using master instrument: (●) calibration, (■) validation and (◆) prediction. NAS: Net Analyte Signal; INT: Interference; RES: Residual.

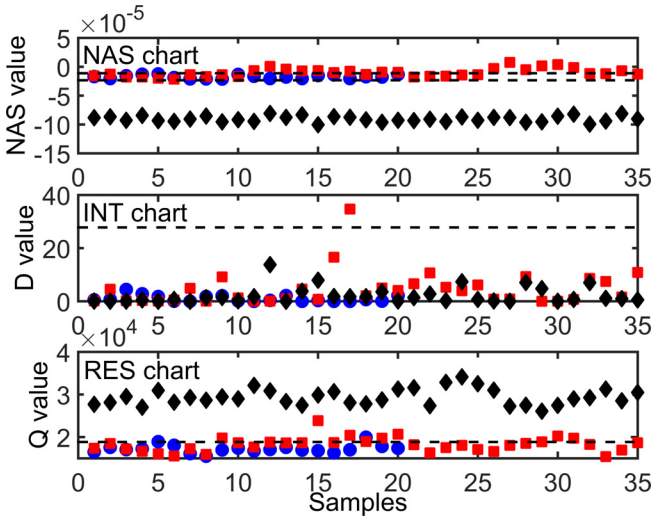

Fig. (7). Control charts for rifampicin using slave instrument: (●) calibration, (■) validation and (◆) prediction. NAS: Net Analyte Signal; INT: Interference; RES: Residual.

CONCLUSION

This paper presents a multivariate control chart transfer approach between two NIR spectrometers for simultaneous determination of rifampicin and isoniazid in pharmaceutical formulation using DS. The study reported herein supports the usefulness and effectiveness of this approach for simultaneous determination of isoniazid and rifampicin using NIR spectroscopy. The results (in terms of correct classification) demonstrated that the direct application of the master instrument to the control charts (NAS, interference and residual) acquired on a slave instrument may lead to poor predictions, making the use of multivariate control chart transfer necessary.

LIST OF ABBREVIATIONS

API	=	Active Pharmaceutical Ingredient
DS	=	Direct Standardization
KS	=	Kennard-Stone
MSC	=	Multiplicative Scatter Correction
MU	=	Model Updating
NAS	=	Net Analyte Signal
NIR	=	Near Infrared
NOC	=	Normal Operating Conditions
O-PLS	=	Orthogonal Projections to Latent Structures
OSC	=	Orthogonal Signal Correction
PDS	=	Piecewise Direct Standardization
PRS	=	Piecewise Reverse Standardization
RS	=	Reverse Standardization
SBC	=	Slope and Bias Correction

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

HUMAN AND ANIMAL RIGHTS

No Animals/Humans were used for studies that are base of this research.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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