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Calibration transfer of near infrared spectrometers for the assessment of plasma ethanol precipitation process

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ABSTRACT

Plasma ethanol precipitation process is an important step in the biopharmacy production process, and near infrared spectroscopy (NIRS) is an effective process analytical technology (PAT) tool in detecting the key quality attribute: the total protein (TP) content. But establishing a robust model is pretty complex. The aim of this study was to explore the calibration transfer strategy between master and slave spectrometers with the biopharmacy. Firstly, 8 batches of ethanol precipitation process were experimented. The changing spectra were collected by two spectrometers, reference values were measured by biuret method. Then, calibration transfer based on the PRS algorithm was carried out. Finally, before establishment of the optimal TP content partial least squares regression (PLSR) model of calibration transfer, rank sample set partitioning based on joint x-y distance (Rank-SPXY) and spectral pretreatment methods were selected after comparison. The determination coefficients of prediction (R_p^2) and root mean squares error of prediction (RMSEP) were 0.934 and 0.8395 g/L, respectively. The results showed that Rank-SPXY-PRS was an effective calibration transfer strategy with different NIRS spectrometers. To some extent, the predictive capability of PLSR model was improved after calibration transfer, and it could provide reference for the further research in biopharmacy production process.

1. Introduction

Plasma ethanol precipitation process is an important step in the manufactories of biopharmacy [1]. Professor Cohn invented the low temperature ethanol precipitation method [2], and formed a complete separation system between human plasma and its proteins in 1946, which has been used by manufactories of blood product all over the world [3]. This method needs to gradually reduce the pH (from 7.0 to 4.0) and temperature (from 2 °C to −2 °C) of the mixed raw plasma, meanwhile increase the ethanol concentration (from 0% to 40%) [4,5]. Finally, a variety of proteins will precipitate from solution, then separate by centrifugation or filtration. If the plasma ethanol precipitation process is not controlled well, such as heat induced or solvent induced phenomena [6], protein degeneration effect would appear and influence the final product. So it is an important step in the production process [7], and total protein (TP) content is the key quality attribute of this process. Manufactories usually complete this process with the fixed time, and detect the TP content of the supernatant last, so as to judge the condition of ethanol precipitation. This method has the shortcoming of time lag, and it unable to guide the production with real-time monitoring.

Near infrared spectroscopy (NIRS), as a process analytical technology (PAT) tool [8,9], has potential applications in the field of pharmaceutical [10,11], food [12] and agriculture [13]. Due to its wide, fast, nondestructive and eco-friendly features [14], NIRS can realize the aim of quantitative and qualitative analysis, non-destructive determination, online or inline inspection and so on [15–17].

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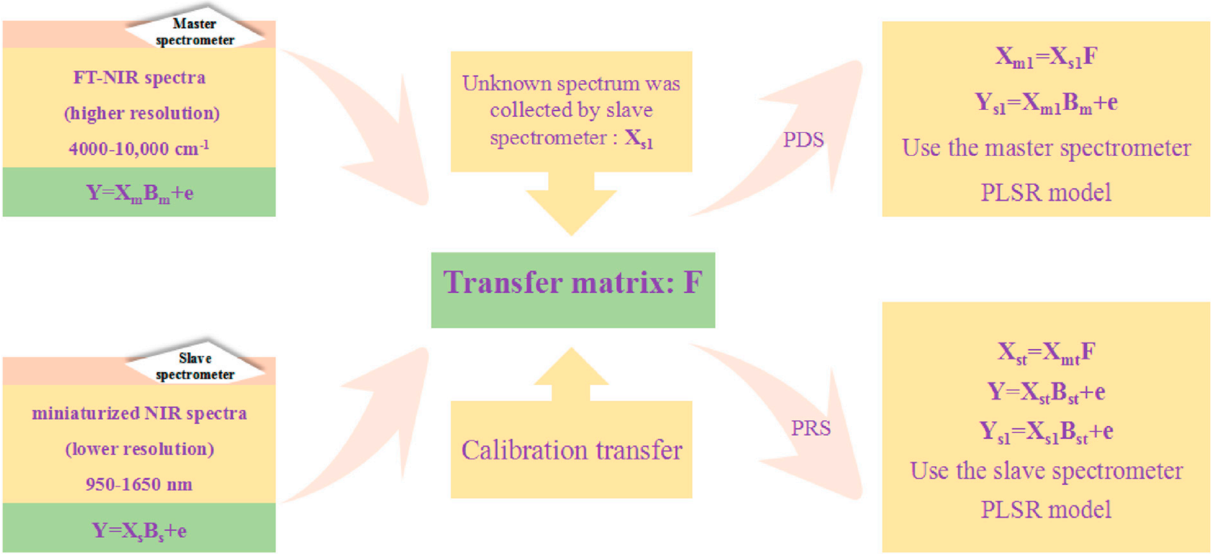

Fig. 1. The calculation principle and comparison of PDS and PRS algorithms.

Fourier transform near infrared (FT-NIR) is a NIRS analytical spectrometer, which is commonly used in the laboratory. It has several advantages, such as high accuracy, good stability and high resolution. Answer relatively to it, it's expensive in maintenance and difficult to apply for the online or inline inspection [18,19]. In recent years, with the requirements of production analysis and engineering development, the miniaturized near infrared (NIR) spectrometers achieve a rapid development [20,21]. Compared with FT-NIR, the miniaturized NIR spectrometer is indeed attractive for application due to its low cost and small volume [22,23]. It also has disadvantages as follows: low sensitivity, poor stability and low resolution [24]. However, the well-known fact that the stability and resolution of FT-NIR spectrometer is better than miniaturized NIR spectrometer [25–28]. But the traditional NIR spectrometer has complex structure with huge volume, it is difficult to be popularized in practical production. The embedded miniaturized NIR could realize the real-time online or in-line monitoring [29] and has a broad development prospect [30].

Multivariate calibration methods of NIRS can be used to realize the rapid and nondestructive detecting in the complex systems, and they have unique advantages in controlling the production process [31,32]. But the NIRS model of the same material can not be used on different spectrometers in the past. In order to improve the applicability of NIRS model, calibration transfer strategy has gradually developed [33,34]. It can transfer spectra from one spectrometer to the same type or different type spectrometer [35]. Through the data processing, calibration transfer strategy can overcome the inconsistency of data in different spectrometers, and improve the dynamic adaptability, prediction capability [36] and precision [37] of the model. Calibration transfer also can reduce the waste in manpower, material, financial resources and time [38,39]. Usually calibration transfer is based on master spectrometer with higher resolution and slave spectrometer with lower resolution [40,41]. The standard calibration transfer algorithms include direct standardization (DS) algorithm [42], piecewise direct standardization (PDS) algorithm [43] and Shenk's algorithm [44].

For FT-NIR and miniaturized NIR, the main differences include baseline drift, wavelength drift and absorbance fluctuations [25,26,45]. The aim of this paper was to transfer the spectra from the master spectrometer (FT-NIR) of higher resolution and stability to slave spectrometer of lower resolution and stability spectrometer (miniaturized NIR), so as to improve the predictive capability of PLSR model in slave spectrometer [46]. But the common method (PDS) only transfer the spectra from slave spectrometer to master spectrometer [43], besides, the wavelength of slave spectrometer was shorter than the maser spectrometer, PDS would bring the unreliable virtual spectra [47]. So it need to “reverse” to bear on this problem. On the contrary, PRS could transfer spectra from master spectrometer (FT-NIR) to slave spectrometer (miniaturized NIR), and the models were established in the slave spectrometer, these method has a noise-filtering effect with multivariate nature [47–49]. The calculation principle and comparison of PDS and PRS algorithms were showed in Fig. 1. Meanwhile, a new samples division method (Rank-SPXY) was proposed. Finally, an effective calibration transfer strategy in monitoring TP content in the plasma ethanol precipitation process with different NIR spectrometers was proved.

2. Materials and methods

2.1. Samples preparation and NIR scanning

The plasma ethanol precipitation process was carried out in the low temperature reactor in the lab, and was corresponded with the manufacturer requirements, only reduced the dosage in proportion. Each batch of plasma was about 100 mL, which had adjusted pH (5.95±0.05) with the acetic acid buffer and placed in a 250 mL round bottomed flask of low temperature reactor. The initial temperature was set at −4.5 °C, when the temperature raised to 0 °C, 95% ethanol solution was added at the speed of 0.875 mL/min with constant flow pump. The plasma ethanol precipitation involved 8 batches, and the processing time of each batch continued about 40 min, liquid samples were collected every two minutes, so 168 samples were obtained. Then centrifuged and filtrated the liquid samples to get the supernatant. The reference TP content values of supernatant were determined with biuret method [50] by AU5800 automatic biochemistry analyzer (Beckman Coulter, USA) in Seriesin Kingmed Diagnostics.

The master spectra of supernatant were collected by FT-NIR (Thermo Fisher Scientific, USA) spectrometer in transmittance mode with a 4 mm pathlength cuvette, 32 scans were set up with the spectral resolution of 8 cm^{-1}. The spectral range of the master spectrometer were 4000–10,000 cm^{-1}. Each sample was collected 3 times at 26 °C with the temperature control component of master spectrometer, and then averaged. While taken air as reference, the background spectra of air were collected every hour.

The slave spectra of supernatant were collected by miniaturized NIR (Viavi, USA) with the following parameters: the spectral range were 950–1650 nm, with 1 mm optical path, and air was also taken as reference, the integral time was 30000 μs? Each sample got 3 spectra when the spectrometer temperature kept at 26 °C, then averaged to reduce errors.