Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy 192 (2018) 437–445

Contents lists available at ScienceDirect

Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy

journal homepage: www.elsevier.com/locate/saa

Comparison of three-way and four-way calibration for the real-time quantitative analysis of drug hydrolysis in complex dynamic samples by excitation-emission matrix fluorescence

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ARTICLE INFO

Article history:
Received 6 October 2017
Received in revised form 15 November 2017
Accepted 22 November 2017
Available online 23 November 2017

Keywords:
Three-/four-way calibration
Real-time quantitative analysis
Excitation-emission matrix fluorescence
Drug hydrolysis
Complex dynamic system

ABSTRACT

Multiway calibration in combination with spectroscopic technique is an attractive tool for online or real-time monitoring of target analyte(s) in complex samples. However, how to choose a suitable multiway calibration method for the resolution of spectroscopic-kinetic data is a troubling problem in practical application. In this work, for the first time, three-way and four-way fluorescence-kinetic data arrays were generated during the real-time monitoring of the hydrolysis of irinotecan (CPT-11) in human plasma by excitation-emission matrix fluorescence. Alternating normalization-weighted error (ANWE) and alternating penalty trilinear decomposition (APTLD) were used as three-way calibration for the decomposition of the three-way kinetic data array, whereas alternating weighted residual constraint quadrilinear decomposition (AWRCQLD) and alternating penalty quadrilinear decomposition (APQLD) were applied as four-way calibration to the four-way kinetic data array. The quantitative results of the two kinds of calibration models were fully compared from the perspective of predicted real-time concentrations, spiked recoveries of initial concentration, and analytical figures of merit. The comparison study demonstrated that both three-way and four-way calibration models could achieve real-time quantitative analysis of the hydrolysis of CPT-11 in human plasma under certain conditions. However, it was also found that both of them possess some critical advantages and shortcomings during the process of dynamic analysis. The conclusions obtained in this paper can provide some helpful guidance for the reasonable selection of multiway calibration models to achieve the real-time quantitative analysis of target analyte(s) in complex dynamic systems.

1. Introduction

Monitoring the dynamic change of chemical parameters and target analytes' concentrations online or real-time is extremely important for the research of drug metabolism, food quality control and degradation of environmental pollutants, etc. For example, monitoring the metabolic transformations of pharmaceuticals is critical to develop safe and effective drugs because most of them can undergo significant metabolic reactions or biotransformations, altering the desired effects of drugs [1]. In addition, the monitoring of many production processes in which some chemical parameters vary over time is the key to comply with quality control regulations. Typical examples are fermentation processes of food or beverages production [2]. However, in most cases, analyses of target compounds are performed off-line by wet chemical assays often involving separation techniques, such as high-performance liquid chromatography (HPLC) or gas chromatography (GC). Unfortunately, these assays require a tedious sample preparation that is usually time- and labor-consuming [2].

The ideal method for online or real-time analysis of dynamic processes should enable direct, rapid, precise, and accurate determination of several target compounds, with minimal or even no sample preparation and reagent consumption. Spectroscopic-based methods might then be a suitable alternative, mainly due to their well-known characteristics, such as non-destructive, rapid and easy automation of measurements. All these features would make spectroscopic-based methods an interesting tool for online or real-time monitoring were it not for the fact that their use in complex media is often hindered by their insufficient selectivity. Fortunately, the developed multiway calibration methods can make up for this deficiency and as an assistant tool combined with spectroscopic-based methods for online or real-time monitoring due to their well-known "second-order advantage", which allows analytes of interest to be quantified even in the presence

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https://doi.org/10.1016/j.saa.2017.11.047
1386-1425/

of uncalibrated interferences. This means that sample cleanup steps are not required or can be reduced. Moreover, only small, pure-analyte calibration sets are required, instead of large and diverse calibration sets containing all possible interferences, to construct calibration model.

These characteristics have promoted the application of multiway calibration methods in the quantitative analysis of target compounds in complex dynamic systems, combined with spectroscopic data [3–10]. Among them, most of the application examples are the combination of excitation–emission matrix (EEM) fluorescence with multiway calibration methods due to the high sensitivity of fluorescence spectroscopy. It is well-known that the EEM data of each sample can be regarded as a two-way data matrix, leading to a three-way data array when the two-way data matrices for a group of samples are joined. Further, a four-way data array can be obtained if an additional time mode was introduced into the measured data set when a kinetic experimental was carried out.

At present, two-way, three-way and higher-way kinetic measurements have been reported in the literature [11–16]. And the first-order and second-order advantage are universally recognized in these reports. Third- and higher-order calibration models include a similar second-order advantage, i.e. the analytes of interest can be quantified even in the presence of unknown interferences. Besides, they may also hold some additional advantages. The mainly proposed candidate properties for the "third-order advantage" were described as follows: 1) decomposition of the third-order data array for a single sample, 2) improved algorithmic resolution of highly collinear data, or 3) increased sensitivity and selectivity [17,18]. However, there is no general consensus on the existence of additional advantages when working with data orders higher than two [17]. Some literature has reported second- and higher-order calibration methods for the resolving of the same dynamic process but without detailed discussions of their advantages and disadvantages [19]. As a matter of fact, how to choose a suitable calibration method for the online or real-time analysis is a troubling problem in practical application. Therefore, comparative study of second- and higher-order calibration methods is urgently needed for the online or real-time monitoring of dynamic processes.

In this paper, as a case, second- and third-order calibration methods were used to resolve the hydrolysis of irinotecan (CPT-11) for real-time quantitative analysis under different temperatures. Based on the spiked recovery of initial concentration, average relative prediction error (ARPE), analytical figures of merit including selectivity (SEL), sensitivity (SEN) and limit of detection (LOD) [20], comprehensive comparisons between second- and third-order calibration methods were carried out. Advantages and disadvantages of second- and third-order calibration methods were discussed detailed for real-time quantitative analysis of the hydrolysis of CPT-11 so as to provide guidance for the reasonable selection of multiway calibration methods to achieve real-time quantitation of target analyte(s) in complex dynamic systems.

2. Theory

2.1. Trilinear and Quadrilinear Models

2.1.1. Trilinear Model of Three-way Excitation × Emission × (Calibration Samples + Kinetic) Data

A spectrofluorometer allows the acquisition of an excitation-emission matrix (EEM) data for one sample by 3D scan. And dynamic processes provide the opportunity of introducing an additional time dimension to the measured data set. Undergoing dynamic process, thus, one sample can generate a three-way data array by following the time evolution of excitation-emission matrices fluorescence spectra. Then, static calibration samples were incorporated into this three-way data array to create a fusion three-way data array $\underline{\mathbf{X}}$ with size of $I \times J \times K$, where I is the number of excitation wavelengths, J is the number of emission wavelengths, and K is the total number of static calibration samples and time points of kinetic samples. This fusion three-way data array $\underline{\mathbf{X}}$ has an internally mathematical structure called trilinearity, in which each element x_{ijk} can be depicted as:

$$x_{ijk} = \sum_{n=1}^{N} a_{in} b_{jn} c_{kn} + e_{ijk}, \quad \text{for } i = 1,2,\ldots,I; j = 1,2,\ldots,J; k = 1,2,\ldots,K \tag{1}$$

where x_{ijk} is an element of the fusion three-way data array of excitation × emission × (calibration samples + kinetic) fluorescence signals; N is the total number of responsive components; a_{in} and b_{jn} are the normalized fluorescence intensities of component n at excitation wavelength i and emission wavelength j, respectively; c_{kn} is the relative concentration of component n in static calibration sample k or time point k; and e_{ijk} is an element of the three-way residual errors array $\underline{\mathbf{E}}$ not fitted by the model.

2.1.2. Quadrilinear Model of Four-way Excitation × Emission × Kinetic × Samples Data

As mentioned above, a given sample produces an $I \times J \times K$ three-way data array during dynamic processes, where I, J, and K denote the number of data points in each of the three dimensions (in EEM-kinetic fluorescence measurements, I is the number of excitation wavelengths, J is the number of emission wavelengths, and K is the number of time data points). Subsequently, calibration sample arrays are incorporated with unknown sample arrays to generate an $I \times J \times K \times L$ four-way data array $\underline{\mathbf{X}}$q (as shown in Fig. 1), where L is the total number of samples. Correspondingly, this four-way data array would have an internally mathematical structure called quadrilinearity, which can be depicted as:

$$x_{ijkl} = \sum_{n=1}^{N} a_{in} b_{jn} c_{kn} d_{ln} + e_{ijkl}, \quad \text{for } i = 1,2,\ldots,I; j = 1,2,\ldots,J; k = 1,2,\ldots,K; l = 1,2,\ldots,L \tag{2}$$

where N is the total number of responsive components; a_{in}, b_{jn} and c_{kn} are the normalized intensities of component n at excitation wavelength i, emission wavelength j and reaction time point k respectively; d_{ln} is the weighted relative concentration of component n in sample l; and e_{ijkl} is an element of the four-way residual errors array $\underline{\mathbf{E}}$q.

2.2. Three- and Four-way Calibration Methods

Two selected three-way calibration methods, alternating normalization-weighted error (ANWE) [21] and alternating penalty trilinear decomposition (APTLD) [22], were used to decompose the fusion three-way excitation × emission × (calibration samples + kinetic) data array. The final quantification of target analytes was achieved based on external calibration procedures, and the scheme of this process can be found in our previous work [3]. Similarly, two four-way calibration methods, alternating weighted residual constraint quadrilinear decomposition (AWRCQLD) [23] and alternating penalty quadrilinear decomposition (APQLD) [24], were selected to decompose the four-way excitation × emission × kinetic × samples data array. Then, a pseudo-univariate calibration curve was established based on the resolved weighted relative concentrations ($\mathbf{D}$) of calibration samples and their nominal initial concentrations. Absolute initial concentrations ($\mathrm{Con}_{t=0}$) of target analytes in the prediction samples were deduced by interpolation of their weighted relative concentrations in the prediction samples into the pseudo-univariate calibration curve. In four-way calibration, the real-time absolute concentration ($\mathbf{Con}_t$) of each analyte can be calculated as $\mathbf{Con}_t = (\mathbf{c}_t/\mathrm{c}_{t=0}) \times \mathrm{Con}_{t=0}$ using the predicted absolute initial concentration ($\mathrm{Con}_{t=0}$) and normalized kinetic profile ($\mathbf{c}_t$). This process was pictorially illustrated in Fig. 1.