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Chemometrics exploration of the kinetics of the reaction between amlodipine and 1,2-naphthoquinone-4-sulfonate

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ABSTRACT

This work presents an exploratory study of the kinetic of the reaction between the drug, amlodipine, and 1,2-naphthoquinone-4-sulfonate (NQS) and gives an interpretation of the kinetic pathway. The kinetic reaction was investigated under pH10.50 and 25 °C by UV–vis spectrophotometric data. Model elucidation was performed by principal component analysis (PCA), multivariate curve resolution-alternating least squares (MCR-ALS) and augmentation of data acquired in different conditions. A data analysis approach based on global hard-modelling was applied to further elucidate the mechanism of the kinetic process, resolve the kinetic and pure spectral profiles of the intermediates and products and evaluate the rate constants. The kinetic process was evaluated with different kinetic two-step consecutive models which their first step was a second-order step. The results of the global hard-modelling of different possible reaction pathways (models) were compared. In spite of the rank deficiency, model parameters in most cases can be obtained by hard-modelling of the single data matrices. However, for some of the kinetic models and experimental conditions, because of the rank deficiency of the concentration matrix, the pure component concentration and spectral profiles cannot be computed since the linear regression step cannot be performed. Here, we applied matrix augmentation to solve this problem.

1. Introduction

Hard-modelling (HM) of multivariate data [1–4], as opposed to independently fitting measurements at single wavelengths has a number of advantages. These include the ability to carry out principal component analysis (PCA) for determination of the number of components in the system [5–9], a more robust fit due to the reduced nonlinear parameter correlation, an improved ability to detect intermediates and the calculation of pure component spectra.

Clearly, HM is preferred relative to soft-modelling (SM) methods like multivariate curve resolution-alternating least squares (MCR-ALS) [10–12] because of its more robust results and more information which can give. The only mandatory prerequisite of MCR-ALS is the inner linear structure of the data. This makes MCR-ALS very flexible to be applied in systems where the model of variation is not known. MCR-ALS can help the process of elucidation of the correct model, i.e., the correct mechanism. This method describes processes without explicitly using the underlying chemical model linked to them. In spite of its simplicity, MCR-ALS can depict a good map of approximate concentration profiles in conditions where our information about the process is very limited. MCR-ALS is able to simply model all the absorbing contributions in the original measurement, i.e., those contributing to the process of interest and those which do not. On the other hand, the most difficult aspect of HM is the determination of the correct model.

The non-linear HM of the experimental data can only be successfully carried out when the kinetic model is known and appropriate. This means that all of the variation in the data collected should be explained by the model.

For determination of the rate constants, without the complete knowledge about the model and the components especially in simple systems, RAFA can be used [13–15]. Apart from its applicability to simple systems [16] and determination of the limited number of parameters, the complete profiles of the components are not resolved. The only advantage of RAFA is its ability to apply to grey systems. In fact, RAFA is able to resolve a portion of a complex system.

Similar to MCR-ALS, when HM approaches are applied to chemical reactions, the robustness of the results will decrease if rank deficiency occurs [17–20]. Rank deficiency occurs when the concentration profiles of absorbing species are linearly dependent because of the requirement of mass balance between the reactants and products. Another cause of rank-deficiency is the so-called rank-overlap. This will occur in a process in which two or more constituents are formed or consumed during the reaction at equal rates, producing concentration profiles of similar shapes.

Global HM of spectral series has shown an optimal performance on many occasions [1,5,6,21,22]. This method allows the simultaneous treatment of several experiments of the same process. Augmentation

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of data taken in different conditions e.g. different mole ratios and analysis by global HM will break rank-deficiency and give well-resolved profiles. The wealth of the information used (several data matrices obtained in different conditions) increases significantly the ruggedness of the results obtained.

It has been reported that 1,2-naphthoquinone-4-sulfonate (NQS) could react with amines and their derivatives due to the fact that lone pairs of electron on nitrogen can attack the electron deficient center in NQS [23], namely the No. 4 carbon atom. This method is used in qualitative identification and quantitative determination of these compounds. The labeling of the amine with NQS is based on a substitution reaction suitable for primary and secondary amines. The actual products of this reaction are not trivial. NQS reacts with primary amines at room temperature to form a complex mixture of products [24]. Although in most cases a one-step kinetic reaction is considered for the reaction of NQS with amine containing compounds, the kinetically formed products are not stable and eventually decompose to other species.

Though numerous applications of NQS as reagent for determination of amine containing compounds by chemometrics methods have been reported [25–28], application of the chemometrics methods to study of its kinetic reaction is rare [15]. In the few reported applications of chemometrics methods, only examining developed chemometrics methods have been the main aim of the researches.

Here, we study the mechanism of the kinetic reaction of drug, amlodipine (AM), with NQS by principal component analysis (PCA), MCR-ALS and global HM. It is important to note that the studies performed so far have focused on the description of the single step of kinetic reaction of an amine compound and have not investigated the potential successive kinetic steps that may take place. Obtaining this information and providing the necessary methodology for this purpose have been the main goal of the present study.

2. Theory

2.1. Multivariate curve resolution-alternating least squares (MCR-ALS)

It is assumed that the spectral response obeys the Beer–Lambert's law. That is, measured absorbance is linearly dependent on the concentration of all absorbing species in a solution.

In spectroscopy, this law can be written as $\mathbf{Y}=\mathbf{CA}+\mathbf{R}$. In many cases, our purpose is to decompose the measured absorbance data matrix $\mathbf{Y}$ ($nt\times m$) into the product of the concentrations $\mathbf{C}$ ($nt\times nc$) and the molar spectra $\mathbf{A}$ ($nc\times m$) of the pure components. In kinetic studies, each row of $\mathbf{Y}$ corresponds to a spectrum at time t recorded at m wavelengths for nc components. Deviations from the product of $\mathbf{C}$ and $\mathbf{A}$ are captured in the matrix $\mathbf{R}$ ($nt\times m$) of residuals.

For applying MCR-ALS to rank-deficient data, it is more suitable to acquire data in different conditions. Data from different conditions are concatenated which give the matrix $\mathbf{Y}_{aug}$ instead of $\mathbf{Y}$. The matrix $\mathbf{Y}_{aug}$ is then decomposed to $\mathbf{C}_{aug}$ and $\mathbf{A}$. The iterative procedure of MCR-ALS can be started with the calculation of the unknown species concentration profiles using the initial estimation of the $\mathbf{A}$ matrix:

$$C_{aug} = Y_{aug}A^{+} \tag{1}$$

where $\mathbf{A}^{+}$ is the pseudo-inverse of $\mathbf{A}$ and is defined as $A^{T}(AA^{T})^{-1}$. In the second stage, a new estimate of the species concentrations is used to calculate the matrix $\mathbf{A}$ by least squares:

$$A = C_{aug}^{+}Y_{aug} \tag{2}$$

where C_{aug}^{+} is the pseudo-inverse of $\mathbf{C}_{aug}$ and is defined as $(C_{aug}^{T}C_{aug})^{-1}C_{aug}^{T}$. These steps are repeated until the data matrix $\mathbf{Y}_{aug}$ is well reconstructed by the calculated $\mathbf{C}_{aug}$ and $\mathbf{A}$ within the experimental error.

The possible unmodeled data variance in the residuals is evaluated by the lack of fit (*lof%*) using the following equation:

$$lof\% = 100 \times \left(\frac{\sum_{i,j}\left(y_{i,j}^{*}-y_{i,j}\right)^{2}}{\sum_{i,j}y_{i,j}^{2}} \right)^{0.5} \tag{3}$$

Where $y_{i,j}^{*}$ and $y_{i,j}$ refer to the calculated and the real absorbance data, respectively.

A series of constraints were applied in an attempt to improve the optimization and to restrict the number of possible solutions. These are: (a) the concentration profiles of each component must be non-negative (nonnegativity) and (b) each concentration profile must have only one maximum (unimodality).

2.2. Global hard-modelling

Global HM requires experiments to be made at a range of initial conditions (generally different initial concentrations. Kinetic HM uses the kinetic rate law to define a system of ordinary differential equations (ODEs) that depend on kinetic parameters, e.g. rate constants. The matrix of concentration profiles $\mathbf{C}_{aug}$ can then be calculated for a given set of rate constants $\mathbf{k}$ ($nk\times 1$) by numerical integration of the ODEs using initial concentrations *i.e.* $\mathbf{c}_0$ ($1\times nc$) [15,29].

In direct kinetic HM of spectroscopic data, originally proposed by Maeder and Zuberbühler [30], the product of the integrated concentration profiles $\mathbf{C}_{aug}$ and the pure component spectra $\mathbf{A}$ is compared to the measured data matrix $\mathbf{Y}_{aug}$. This results in the residuals $\mathbf{R}=\mathbf{Y}_{aug}-\mathbf{C}_{aug}\mathbf{A}$ which captures the differences between the measured and the modelled absorbances. In the least-squares analysis, the sum of all squared residuals *i.e. ssq* is used as the objective function to be minimized by iteratively optimizing the rate constants, $\mathbf{k}$. Here, the Newton–Gauss–Levenberg/Marquardt algorithm (NGL/M) was used to solve the non-linear regression [1,29–33]. This gradient-based method allows estimating the uncertainties in the optimized rate constants from the variance/covariance matrix [34].

Since $\mathbf{A}$ is comprised of linear parameters only, it can be eliminated from the non-linear optimization by regressing the spectroscopic data on the concentration matrix using Eq. (2) at each iteration [35]. In this way, the residuals and the sum of their squares can be defined as a function of the nonlinear parameters, $\mathbf{k}$. In these conditions, we can write $\mathbf{R}=f(\mathbf{Y}_{aug},\mathbf{k})$.

3. Experimental

3.1. Apparatus and software

An Agilent 8453 UV–vis spectrophotometer with diode array detector was used for recording of the absorption spectra in the spectral range of 220–600 nm. A Huber polystat model CC3 thermostat was employed for temperature controlling. All pH measurements were made with a Jenway 3345 ion meter supplied with glass combination electrode.

The treatment of the absorption spectral data was performed in MATLAB 6.5 environment (MATLAB 6.5, The Mathworks Inc., Natick). A series of m-files written in MATLAB environment were used to perform multivariate HM. Kinetic data were also analyzed by MCR-ALS method. This method is implemented in a small set of MATLAB functions [36].

3.2. Reagents and solutions

All chemicals were of analytical grade and used as received without any further purification. These were NQS (Merck, >99%) and AM. Structural formulas of NQS and AM have been shown in Fig. 1.