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Self-modeling curve resolution method applied for the evaluation of dissolution testing data: A case study of meloxicam–mannitol binary systems

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ABSTRACT

This paper introduces some chemometric methods, *i.e.*, self-modeling curve resolution (SMCR), multivariate curve resolution-alternating least squares (MCR-ALS) and parallel factor analysis (PARAFAC and PARAFAC2), which are used to evaluate *in vitro* dissolution testing data detected by a UV–vis spectrophotometer on meloxicam–mannitol binary systems. These systems were chosen because of their relative simplicity to apply as part of the validation process illustrating the effectiveness of the developed and applied chemometric method. The paper illustrates the failure of PARAFAC methods used before for pharmaceutical data evaluations as well, and we suggest application of the feasible band form given by SMCR as a more general procedure.

Steps to improve the dissolution behavior of drugs have become among the most interesting aspects of pharmaceutical technology, and our results show that a larger particle size of meloxicam is advantageous for dissolution. Instead of the use of only one characteristic wavelength, appropriate chemometric methods can furnish more information from dissolution testing data, *i.e.*, the individual dissolution rate profiles and the individual spectra for all the components can be obtained without resorting to any separation techniques such as HPLC.

1. Introduction

In the pharmaceutical industry, the development of a new drug involves not only the discovery of a new biologically active agent, but also the physico-chemical development of a stable form of the active ingredient and the pharmaceutical development of an effective pharmaceutical dosage form. The determination of dissolution properties is one of the most commonly performed solid dosage form assays in the pharmaceutical industry and is used to establish the release profiles of solid dosage forms (tablets or capsules) in an *in vitro* system. In traditionally performed dissolution tests using baskets (apparatus 1) and paddles (apparatus 2), a dosage form unit is placed in a stirred, thermostated vessel and samples are removed at regular intervals and analyzed by a standard analytical chemistry method, *e.g.*, spectrophotometrically at a suitable chosen wavelength in the UV–vis region [1].

The history of dissolution testing processes started in 1897 with the paper of Noyes and Whitney [2]. They established that "the rate at which a solid substance dissolves in its own solution is proportional to the difference between the concentration of that solution and the concentration of the saturated solution" and gave the first mathematical expression of a diffusion-controlled dissolution process.

There are several factors that are known to influence the rate of dissolution of a pharmaceutical product *in vitro* [3], including pH, temperature, agitation, etc. Since 1967, USP has regularly standardized dissolution tests, prescribing the appropriate parameters and recommending the two apparatuses [4]. As an indication of the progress that has been made, computerized and automated systems have been developed [5,6]. Through the use of simple or multiple fiberoptic probes [7–11] and multi-wavelength sensors [12,13], chemometric methods can be applied for data analysis [14–19].

Wiberg and Hultin [20] recently reported on the application of chemometric methods to fiberoptic dissolution testing data on glibenclamide tablets enclosed in hard gelatin capsules. Their study did indeed contain applications of several chemometric methods (PLS, MCR-ALS, and GRAM) which all gave quite accurate estimations of the pure spectra and dissolution profiles. However, in their PARAFAC application some discrepancies seemed to be found, below we discuss the possible reason and the solution.

In the present case study, meloxicam–mannitol binary systems were used to investigate how chemometric methods can be used to evaluate dissolution testing data. The systems were chosen because of their relative simplicity. We used them as proper controlling systems to validate our developed and used chemometric methods.

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First we tried PARAFAC (because Wiberg and Hultin [20] reported its usefulness for dissolution studies) to evaluate the data measured with the standard condition, *i.e.*, using juice in the reference cell. In that case negative absorbances occurred, thus self-modeling curve resolution (SMCR) method could not be used; the minimal non-negativity condition for SMCR was not fulfilled. We replaced the reference material to distilled water, and in that case only non-negative absorbances were obtained, thus PARAFAC and SMCR methods could become comparable. This paper is a natural continuation of our previous study [21]. The theme of this paper is not intended to be industrial, we prepared all substances under laboratorial circumstances.

2. Theoretical background

2.1. Meloxicam and mannitol as model materials

Meloxicam (ME; 4-hydroxy-2-methyl-N-(5-methyl-2-thiazolyl)-2H-benzothiazine-3-carboxamide-1,1-dioxide) is one of the enolic acid class compounds of nonsteroidal anti-inflammatory drugs (NSAIDs). ME selectively inhibits COX-2 more than COX-1 [22], and it has recently been used in the treatment of rheumatoid arthritis, osteoarthritis, Alzheimer's disease and cancers (mainly colorectal cancers) [23].

Because of the very low solubility of ME in acidic media, it can cause few adverse local gastrointestinal events [22] and this is one of its main advantages (other advantages such as good renal tolerability have been reported) [24]. One way to improve solubility is to disperse a drug in a carrier, either as a eutectic mixture or as a simple solid dispersion (physical mixtures, PMs) [25].

Mannitol ($C_6H_{14}O_6$), a sugar alcohol, is widely used in the pharmaceutical and food industries [26]. Mannitol is a water-soluble material: according to US Pharmacopoeia (USP) [1] 1 g dissolves in 5.5 ml of water. In the present experiment, β-D-mannitol was used as a carrier to increase the solubility of ME.

2.2. Self-modeling curve resolution with non-negativity constraints

SMCR, one of the oldest chemometric procedures, was introduced for two-component systems by Lawton and Sylvestre [27] (LS) in 1971 to deconvolve raw spectroscopic data into the product of two physically interpretable profile matrices, provided that both concentrations and absorbances are non-negative, accepting both as minimal constraints. Unfortunately, the solution is not unique; without further restrictions, the method can give only feasible regions for the pure component profiles. Later, Borgen et al. [28,29] generalized the LS method for three-component systems with the same minimal constraints. The concepts of Borgen seemed to be rather difficult to understand and to implement, and hence several chemometricians turned to the development of approximation methods [30]. Rajkó and István [31] recently have revisited Borgen's method, gave a clearer interpretation and used computational geometry tools to find inner and outer polygons. Rajkó [32] has subsequently extended the duality concept to the minimal constrained SMCR making a simpler algorithm possible.

2.3. Decomposing two-way bilinear data

The spectroscopic data can be collected into a two-way data type, *i.e.*, the response matrix $\underset{I\times J}{\boldsymbol{R}}$. Every *i*th row represents an object (the spectrum of a sample) and every *j*th column a variable (generally, a composition profile). According to the Bouguer–Lambert–Beer Law, the matrix will be the product of two matrices, $\underset{I\times N}{\boldsymbol{C}}$ (concentration profile matrix) and $\underset{J\times N}{\boldsymbol{S}}$ (spectral profile matrix), built up with the profiles of the individual *N* components:

$$\underset{I\times J}{\boldsymbol{R}} = \underset{I\times N}{\boldsymbol{C}}\,\underset{N\times J}{\boldsymbol{S}^{\mathrm{T}}} = \sum_{n=1}^{N} \boldsymbol{c}_n\,\boldsymbol{s}_n^{\mathrm{T}} \qquad (1)$$

Of course, we cannot know the concentration profiles in advance; in fact the task is to exploit them from the measured data with the help of SMCR methods, presuming only minimal restrictions, but without any estimation of parameters of any predefined model functions. Singular value decomposition (SVD) [33] can be regarded as the basic procedure of the chemometric methods and SMCR methods are also based on SVD.

The bilinear data matrix $\underset{I\times J}{\boldsymbol{R}}$ can be decomposed into orthogonal product matrices by SVD or principal component analysis (PCA) [34,35]:

$$\underset{I\times J}{\boldsymbol{R}} = \left(\underset{I\times N}{\boldsymbol{U}}\,\underset{N\times N}{\boldsymbol{D}}\right)\quad \underset{N\times J}{\boldsymbol{V}^{\mathrm{T}}} = \underset{I\times N}{\boldsymbol{X}}\,\underset{N\times J}{\boldsymbol{V}^{\mathrm{T}}}, \qquad (2)$$

where **U** is the matrix with the left eigenvectors of **R** in its columns, **D** is the diagonal matrix of the singular values, **V** is the matrix with the right eigenvectors of **R** in its columns, and in terms of the PCA: **UD** = **X** is the score matrix and **V** is the loading matrix.

The suitably chosen initial estimations of **S** or **C** are optimized by solving Eq. (1) iteratively by alternating least squares (ALS) optimization:

$$\begin{aligned} \underset{N\times I}{\boldsymbol{C}^{+}}\cdot\underset{I\times J}{\boldsymbol{R}} &= \underset{N\times J}{\boldsymbol{S}^{\mathrm{T}}} \\ \underset{I\times J}{\boldsymbol{R}}\cdot\underset{J\times N}{(\boldsymbol{S}^{\mathrm{T}})^{+}} &= \underset{I\times N}{\boldsymbol{C}} \end{aligned} \qquad (3)$$

where $^+$ means the pseudoinverse [36].

Unfortunately, this decomposition is often not unique because of the rotational and intensity (scaling) ambiguities [27–31,35,37]. The rotational ambiguities can be moderated or even eliminated if convenient constraints can be used [38–41]. Tauler and de Juan developed a Matlab code for MCR-ALS [42] with some constraints, *i.e.*, non-negativity, unimodality, equality and closure. The same algorithm has been implemented in the PLS_Toolbox [43], offering only non-negativity and equality constraints. Gemperline and Cash presented another method, called GUIPRO P-ALS, using least squares penalty functions [44] to implement constraints in an ALS algorithm.

In this paper, acronym SMCR is used for the algorithm with which analytical band solution can be obtained, and acronym MCR-ALS is used for the approximation method which can provide "unique" solution (at least in mathematical sense: after the convergence, the solution will be the same using different initial values; of course this "unique" solution will be only one from the feasible regions/band solution).

2.4. Decomposing three-way trilinear data

When several dissolution tests of related samples are analyzed, the data can be arranged in a three-way data cube. Parallel factor analysis (PARAFAC) [35,45–48] can decompose this data cube (dissolution times by wavelengths by samples) if the data are trilinear and the dissolution rate profiles and spectral profiles to be calculated remain the same in every run. According to this, the working equation of PARAFAC is:

$$\underset{J\times K}{\boldsymbol{R}_i} = \underset{J\times N}{\boldsymbol{S}}\cdot\underset{N\times N}{\boldsymbol{Q}_i}\cdot\underset{N\times K}{\boldsymbol{E}^{\mathrm{T}}}\quad \underset{N\times N}{\boldsymbol{Q}_i} = Diag\left(\boldsymbol{c}_{i,1:N}\right)\quad i = 1\ldots I \qquad (4)$$

where $\mathbf{R}_i$ is the matrix of the *i*th slice of the data cube $\underline{\mathbf{R}}$, **E** is the matrix of dissolution rate profiles, **S** is the matrix of spectra, and $\mathbf{Q}_i$ is a diagonal matrix with the elements of the *i*th row of matrix **C** in its diagonal, whereas **C** is the matrix of concentration profiles