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Blending process modeling and control by multivariate curve resolution

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ABSTRACT

The application of the Multivariate Curve Resolution by Alternating Least Squares (MCR-ALS) method to model and control blend processes of pharmaceutical formulations is assessed. Within the MCR-ALS framework, different data analysis approaches have been tested depending on the objective of the study, *i.e.*, knowing the effect of different factors in the evolution of the blending process (modeling) or detecting the blend end-point and monitoring the concentration of the different species during and at the end of the process (control).

Data analysis has been carried out studying multiple blending runs simultaneously taking advantage of the multiset mode of the MCR-ALS method. During the ALS optimization, natural constraints, such as non-negativity (spectral and concentration directions) have been applied for blend modeling. When blending control is the main purpose, a variant of the MCR-ALS algorithm with correlation constraint in the concentration direction has been additionally used. This constraint incorporates an internal calibration procedure, which relates resolved concentration values (in arbitrary units) with the real reference concentration values in the calibration samples (known references) providing values in real concentration scale in the final MCR-ALS results.

Two systems consisting of pharmaceutical mixtures of an active principle (acetaminophen) with two or four excipients have been investigated. In the first case, MCR results allowed the description of the evolution of the individual compounds and the assessment of some physical effects in the blending process. In the second case, MCR analysis allowed the detection of the end-point of the process and the assessment of the effects linked to variations in the concentration level of the compounds.

1. Introduction

Blending processes are of utmost importance in the industrial production of pharmaceuticals or food commodities [1–4]. The Quality by Design paradigm promotes the use of process analytical technologies to help assess in real time, the state of a unit operation. Pharmaceutical Quality by Design (QbD) is a "systemic approach to pharmaceutical development that begins with predefined objectives and emphasizes product and process understanding and process control" [5,6]. Blending is critical in ensuring uniformity of composition in the final dosage form, as part of the multiple unit-operations involved in the manufacturing process of pharmaceutical solid dosage forms [7,8]. Problems incurred during blending can lead to inadequate tablet quality attributes such as content uniformity, assay, disintegration time, dissolution behavior, *etc.*, all of which can directly impact dosage form efficacy, in-vivo performance, and patient safety. Controlling blend homogeneity is a necessary step in a drug product manufacturing process [9]. When a blend process is analyzed, two main objectives can be of interest: first, optimizing the process parameters to improve the blending operation and, second, detecting when the blend process has reached an homogeneity standard set by external regulations or by the manufacturer [10–13]. The first objective requires modeling the blend process, *i.e.*, describing how the variation of experimental conditions can affect the evolution of the blending profiles (trajectories) of the compounds in the production system, whereas the second calls for blend control, *i.e.*, obtaining quantitative information on the process (concentration values of blended compounds) that allows deciding when the blend end-point, or homogeneity, has been reached.

Multivariate Curve Resolution-Alternating Least Squares (MCR-ALS) is a chemometric method that has been widely used for process analysis in industrial, biological or chemical contexts [14–20]. The term process here must be interpreted as any continuous physical/chemical transformation that can be monitored by an instrumental

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response. This includes from classical reaction systems, to chromatographic elutions or to physical changes, such as blending or polymorph transitions [21,22]. Classical MCR-ALS acts as a soft-modeling approach on the raw process (spectroscopic) data to provide concentration profiles, *i.e.*, the evolution of the compounds involved in the process as a function of the control variable (time, pH, temperature …), and their related pure spectra. In this situation, the inclusion of knowledge about the system in the form of natural constraints (non-negativity in the concentration and spectral profiles, unimodality, closure, …) is enough to drive the resolution to optimal solutions from both mathematical and chemical viewpoints [23]. When the underlying physicochemical model driving the process is known, this information can also be included on the hybrid variant of the algorithm incorporating hard-modeling information [24].

Classical MCR provides concentration profiles and pure responses of the compounds involved in a process in arbitrary units. However, in some situations, it is interesting to obtain quantitative information in addition to the qualitative one. In order to obtain this supplementary information, the application of a variant of the MCR-ALS algorithm with a correlation constraint is needed, in which an internal calibration model is built relating the real concentration values of calibration samples to the ones in arbitrary units provided by the constrained least-squares calculated concentration profiles during the MCR optimization procedure [25–28]. The model established helps to rescale the concentration values found by the resolution algorithm (in calibration and test samples) to the real concentration units during the iterative optimization. In this way, the final concentration profiles provided by MCR-ALS with the correlation constraint include quantitative information comparable to that furnished by other multivariate calibration methods.

The quantitative information provided by the new correlation constraint can be especially useful to control processes in industrial environments, in which either the normal operation conditions or the final product quality are very well defined in quantitative terms. An example of this kind is the blending process of pharmaceutical formulation, in which there is a complete knowledge about the individual components that will form the mixture and compliance of nominal composition and homogeneity is required before proceeding to the compression of the sample into the commercial tablet form.

Control of the composition of the mixture was traditionally carried out by sampling from the blender and, then, performing an *ex situ* quantitative analysis until the homogeneity/composition standards was fulfilled [29–31]. Nowadays, continuous *in situ* sampling using NIR probes that allow obtaining immediate knowledge regarding the blending process are being developed [32,33]. However, it is necessary to apply data analysis methods that can work efficiently with these multivariate data sets. In the literature, several methods can be found to monitor the variations that occur in the mixture and to determine the end-point of the blending process according to certain criteria [2,11,31,33].

This paper proposes the use of Multivariate Curve Resolution by Alternating Least Squares method for the double purpose of modeling and controlling the blending of a solid pharmaceutical formulation.

Modeling of the blending trajectories allows assessing the effect of modifying process control variables (filling of the blender, rotation speed …) and can be carried out by classical MCR using natural constraints in a calibration-free mode. This information can be gathered from the evolution and shape of the blending concentration profiles (in arbitrary units).

Control of the blending run (composition along the run and detection of the end-point of the process) is obtained when MCR is used with the correlation constraint that allows recovering quantitative information. In this case, the blend concentration profiles are obtained in real concentration units. Within the quantitative approach, several variants of application will be tested that simulate both *ex situ* (after the run is over) and *in situ* (for ongoing runs) control, or compound-specific and global homogeneity detection that are of interest from an industrial point of view.

2. Materials and methods

2.1. Experimental work

Five components were used in the different formulations: acetaminophen (APAP; Rhodapap, Rhodia Organique, Roussillon, France), lactose (monohydrate NF – product 316/Fast-Flo modified spray-dried; Foremost Farms USA, Rothschild, WI, USA), microcrystalline cellulose (MCC; Avicel PH 200, FMC Biopolymer, Mechanicsburg, PA, USA), croscarmellose sodium (cros, Spectrum, Gardena, CA, USA) and magnesium stearate (MgSt; Mallinckrodt, Hazelwood, MO, USA).

Ingredients were mixed simultaneously in a 3.5 quart, stainless steel, custom-made V-blender. A SpectralProbes Process NIR spectrometer (Thermo Fisher Scientific, Wilmington, MA, USA; serial numbers 1277) was used to monitor the blending process in real-time acquiring one spectrum every 4 s if rotation speed is 15 rpm and every 2.4 s if rotation speed is 25 rpm. Measurements were made through a sapphire window in the top of an arm of the blender. Spectra were sent wirelessly to a computer and imported into a custom-made acquisition and analysis software. NIR spectra were formed by 100 absorption values between 1600 and 2400 nm in reflectance mode and the probe was triggered by a light intensity sensor. For further information of the experimental details, the readers are referred to previous works [11,12].

2.2. Sample sets

Two different data sets have been used in this work. First, a three-component system (one active principle, APAP, and two excipients, MCC and MgSt) has been considered. This system has been used to study the ability of MCR-ALS to model blend processes and to identify physical effects related to the blend evolution. The experimental design, a 4-factor 2-level full factorial design (Table 1) included as factors: the concentration level of the active principle (APAP) in the formulation (3% or 30%); the rotation speed of the blender (15 or 25 rpm), the fill level of the blender (50% or 70%), and the ingredients loading mode (side to side or top to bottom).

Second, a five-component system (one active principle, APAP, and four excipients, lactose, MCC, cros and MgSt) has been studied to assess the ability of MCR-ALS to detect the end-point of the blending process and, in general, to perform quantitative blending control. In this case, Table 2 shows 7 runs with a large range of concentrations for APAP (five concentration levels: 21.0%, 25.5%, 30.0%, 34.5% and 39% w/w) and three lactose:MCC ratio levels (0.4, 1.4 and 2.4). In this case, the amount of croscarmellose sodium and magnesium stearate has been the same in all the batches since they act just as agglutinants. Additionally, two more runs were used as test runs mimicking the concentration level of the target formulation: APAP 30%, lactose 37.3% and MCC 26.7% (lactose:MCC ratio equal to 1.4).

2.3. Chemometric analysis

2.3.1. Data pretreatment

In this work, experimental spectra have been pretreated by means of Multiplicative Scatter Correction (MSC) prior to the chemometric analysis [34].

This pretreatment method gives an estimation of the relation of the scatter of each sample with respect to the scatter of a reference