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An eco-friendly strategy, using on-line monitoring and dilution coupled to a second-order chemometric method, for the construction of dissolution curves of combined pharmaceutical associations

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ABSTRACT

A simple, precise, economic and minimally operator-dependent method was developed under green analytical chemistry principles, for the simultaneous construction of the dissolution curves of a pharmaceutical association in short time and without employing organic solvents, allowing important savings of labor and resources. The carvedilol (CAR) and hydrochlorothiazide (HCT) combined formulation was employed as a model. The method (OD/UV-MCR) involves on-line sample dilution (OD) and UV detection of the analytes, coupled to multivariate curve resolution with alternating least squares (MCR-ALS).

OD/UV-MCR proved to be robust and was successfully validated in accordance to ICH guidelines, fulfilling acceptance criteria for specificity (r^2 of spectral correlation > 0.950), linearity [$r > 0.999$ ($N = 25$) in the ranges 1.00–31.1 mg l^{-1} and 0.51–15.2 mg l^{-1} for CAR and HCT, respectively] and precision (RSD < 2%). Accuracy was assessed by point-to-point comparison between the dissolution profiles furnished by the proposed method with those provided by HPLC analysis, evidencing the usefulness of this monitoring system.

In addition, OD/UV-MCR was successfully employed for the comparative analysis of three lots of commercial formulations of the CAR–HCT pharmaceutical association, belonging to a couple of different brands, employing Moore and Flanner's f_2 similarity indicator.

1. Introduction

In vitro dissolution testing has become a relevant strategy for assessing the performance of solid oral dosage forms. Construction of dissolution profiles of pharmaceutical formulations is currently an established operation, contained in modern pharmaceutical regulations [1–4].

The dissolution profiles gain significance because they are suitable for estimating the availability of the active ingredients and as critical means of assessing the similarity between innovator and generic products for exchangeability purposes [5]. They are also useful guides during the development of new formulations, being employed to control the lot-to-lot consistency during the manufacturing process [6], and serving to confirm its reproducibility after changes in location, equipment, lot size and other key manufacturing parameters [1,7,8].

Green chemistry is an established working paradigm which pursues eco-friendliness of chemical activities, by focusing on preventing pollution caused by chemicals. Its principles include diminishing contaminating wastes, using safer solvents and performing analysis in real time. Accordingly, green analytical chemistry strategies involve direct measurement of untreated samples, replacement of toxic reagents and automation [9].

Fixed-dose pharmaceutical associations are a special case of combination products, which are advantageous in terms of better therapeutic efficiency, reduced adverse effects, convenience of dose and improved patient compliance. However, their dissolution profiling for quality control purposes faces some practical challenges [10], including the need of carrying out the simultaneous quantification of their active principles in several samples, in a wide range of analyte concentrations and under cost-effective conditions. Furthermore, performing this operation without any physical separation step entails an additional hurdle, due to the possibility of mutual interference of the formulation ingredients.

Different chromatographic, electrophoretic and spectroscopic approaches have been developed in recent times toward the elaboration of dissolution profiles of drug associations [11,12]. The

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first group is based mainly on HPLC; however, this methodology requires skilled manpower and demands the use of significant amounts of organic solvents, being also time-consuming, poorly eco-friendly and not very cost-effective.

The second alternative is represented by capillary electrophoresis (CE) [13]; however, it also entails sample conditioning and the use of expensive equipment. In addition, CE methods often suffer from problems of reproducibility and, as for the HPLC determinations, measurements cannot be carried out on-line.

The third choice involves using spectroscopic means. Despite being fast and their use inexpensive, they are sensitive to interferences due to the presence, in the dissolution medium, of other absorbing active ingredients or excipients from the dosage form under test.

Some of these drawbacks can be overcome by chemometrics processing of the spectroscopic signals. Although NIR, Raman and IR spectroscopies have been employed for monitoring drug dissolution [14–16], UV–vis is the most used spectroscopic approach. We and others have developed UV-chemometric strategies to the point-by-point acquisition of dissolution curves and dissolution profiles from pharmaceutical associations [17].

However, in order to deal with the wide range of analyte concentrations in the dissolution samples, different treatments were employed, including sample dilutions [18], use of multiple calibrators [19] and asymmetric calibration designs [20], rendering the overall strategy too laborious, hence time-consuming, less user-friendly and more prone to errors.

The association between fiber optics and UV–vis detection [21,22], an alternative which became an area of interest in dissolution testing technology since it enables on-line monitoring of the process, has attracted attention among the pharmaceutical analysts and has found some use for the elaboration of dissolution curves of drug associations [23]. However, the fiber-optics setups demonstrated not to be versatile enough to deal with the scatter produced by undissolved materials and with detector saturation due to high analyte concentrations.

Recently, we have also reported a simple and efficient on-line monitoring strategy for the simultaneous construction of two dissolution curves from a binary drug association, entailing a closed circulation system with a flow cell associated to a UV–vis detection system, and a chemometrics application for data analysis (UV-MCR-ALS) [24]. However, we have observed that this experimental setup is not general. One of its important practical limitations becomes evident when high concentrations of the analytes must be quantified; in these cases, the direct determination of the active principles in the dissolution media is hindered by detector saturation or impeded by lack of linearity of the detector response. In these cases, signal adjustment becomes mandatory.

One of such scenarios is the dissolution testing of the carvedilol (CAR) and hydrochlorothiazide (HCT) association (Fig. 1), where loss of linearity followed by detector saturation, only allows unattended monitoring of the initial stages of the dissolution.

The CAR–HCT association, which combines a non-cardioselective β-adrenergic blocker [25] and a benzothiadiazine diuretic, respectively, has been patented for the treatment of cardiac and cardiovascular disorders, such as hypertension, angina pectoris and cardiac insufficiency [26]. The combination is indicated when the monotherapy fails to achieve arterial blood pressure normalization. However, CAR is poorly soluble (0.02 mg ml^{-1} at pH 7.4) and the association must be administered in very carefully adjusted doses for each patient; hence, dissolution studies are needed to guarantee manufacturing consistency and that proper amounts of the drugs are made bioavailable.

The simultaneous quantification of CAR and HCT has received much attention, and several spectrophotometric [27–29] and chromatographic [30,31] methods have been reported for that purpose

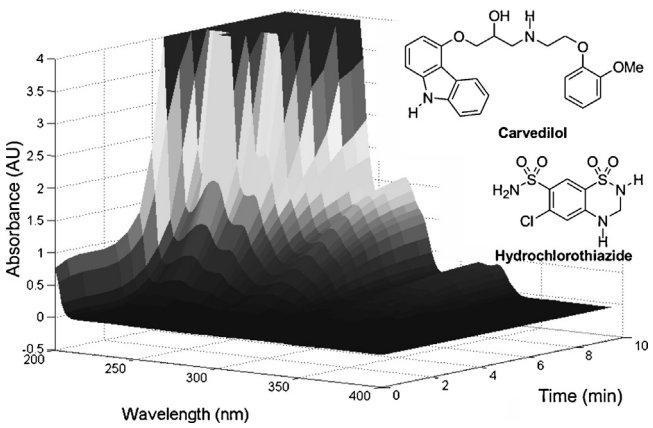

Fig. 1. Chemical structures and 3D graphical representation of the dissolution process of tablets containing the CAR–HCT association employing the system described in Ref. [21].

in combined dosage forms or in biological fluids [32,33]; however, while the former are not very well suited for dissolution testing purposes, the latter require sophisticated equipment and were designed for aims other than routine pharmaceutical quality control.

Therefore, as a natural evolution of our previous study, herein we report the development and validation of a simple and efficient chemometrics-assisted alternative for the on-line monitoring of the pharmaceutical dissolution of a drug association, especially when the amounts of the dissolved drugs saturate the detector.

The strategy (OD/UV-MCR), which complies with green analytical chemistry principles and strategies, and allows the simultaneous construction of the dissolution curves of the active components, is based on performing on-line sample dilution and requires minimal operator intervention. The association between CAR and HCT was employed as an example.

2. Materials and methods

2.1. Reagents

2.1.1. Chemicals

All the experiments were performed with pharmaceutical-grade CAR and HCT. HPLC-grade acetonitrile (ACN) was acquired from Panreac (Barcelona, Spain). Water was obtained from a Milli-Q system (Millipore, Bedford, USA) and was employed for HPLC experiments and for preparing the samples and dissolution media. All other chemicals were of analytical grade and were used as received. Three lots of tablets (A_1, A_2 and B) belonging to two different brands of the commercial CAR–HCT association (25 mg CAR and 12.5 mg HCT) were acquired in a local pharmacy.

2.1.2. Sample preparation

Stock standard solutions of CAR (5020 mg l^{-1}) and HCT (2530 mg l^{-1}) were independently prepared in 10 ml volumetric flasks, by dissolving accurately weighed amounts of the drugs in methanol. Working solutions (100.4 mg l^{-1} for CAR and 50.6 mg l^{-1} for HCT) were prepared by transferring appropriate volumes of the stock solutions to separate 50 ml volumetric flasks and diluting to their marks with 0.1 N HCl.

Two sets of five calibration samples each were prepared in volumetric flasks, by mixing appropriate volumes of the working solutions of the drugs and diluting to the mark with 0.1 N HCl. The concentration levels obtained for CAR were 1.00, 8.03, 16.1, 24.1 and 31.1 mg l^{-1} and those for HCT were 0.51, 2.02, 8.10, 12.1 and 15.2 mg l^{-1}.