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A Review of chemometrics assisted U.V. spectroscopy of pharmaceutical dosage form

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1. ABSTRACT

Chemometrics is a branch of science that derives data by the application of mathematical and statistical methods, for the extraction of useful information from physical and chemical phenomena involved in a manufacturing process. Chemometrics is used for multivariate data collection and analysis protocols, calibration, process modelling, pattern recognition and classification, signal correction and compression, and statistical process control. Both predictive and descriptive issues of life sciences could be solved by chemometrics. Chemometrics is a branch of science that derives data by the application of mathematical and statistical methods, for the extraction of useful information from physical and chemical phenomena involved in a manufacturing process. Chemometrics is used for multivariate data collection and analysis protocols, calibration, process modelling,

2. INTRODUCTION

Chemometrics is a branch of science that derives data by the application of mathematical and statistical methods, for the extraction of useful information from physical and chemical phenomena involved in a manufacturing process. Chemometrics is used for multivariate data collection and analysis protocols, calibration, process modelling, pattern recognition and classification, signal correction and compression, and statistical process control. Both predictive and descriptive issues of life sciences could be solved by chemometrics. Chemometrics is a branch of science that derives data by the application of mathematical and statistical methods, for the extraction of useful information from physical and chemical phenomena involved in a manufacturing process. Chemometrics is used for multivariate data collection and analysis protocols, calibration, process modelling,

pattern recognition and classification, signal correction and compression, and statistical process control. Both predictive and descriptive issues of life sciences could be solved by chemometrics[1-3]

The first applications of flow methods to multi-component analysis were reported in the 1980s with publication of methods for quantification of drug mixtures in aqueous samples and pharmaceuticals.[4-6] As interferences from the sample matrices were almost negligible, each compound was quantified easily from enzymatic reactions or kinetic discrimination of components. Since then, significant advances in this topic have been achieved.[6-8] Special attention has been paid to the development of strategies for obtaining selectivity as well as expanding the range of applications towards more complex matrices. The analysis of clinical, biochemical and food samples generally requires sophisticated pretreatments prior to quantification of the active compounds.[6, 9] As a result, on-line implementation of auxiliary chemical operations(e.g., solid-phase extraction, liquid-liquid extraction, dialysis, gas-diffusion, and derivatization) becomes especially relevant[6, 10]

Modelling a phenomenon either to describe or interpret provides an in depth understanding
beyond the reach of human thinking. The two fundamental types of models generally used are theoretical and empirical. At variance with the former, empirical models do not adhere to any theoretical basis and are data-driven. Chemometrics, the science of relating measurements made on chemical systems or processes to their state via application of mathematical and statistical modelling[11] has become a well-recognized sub-discipline in contemporary analytical chemistry. The advances in high performance liquid chromatography (HPLC) analytical strategies, driven by several variables, provide large amount of data during the course of analytical measurements. Although HPLC is a versatile separation technique with wide range of applications, the process is sometimes critical due to its large number of variables, which need to be properly adjusted before every single run. Consequently, the necessity emerges for a deeper understanding of such methods. Chemometric tools with suitable statistical analysis have become popular by the way, considering multiple advantages viz. reduction in the number of experiments and lower reagent consumption and less laboratory work. Furthermore, optimization of HPLC methods are complex processes; since, several variables (mobile phase pH, buffer concentration, flow rate, column temperature, detector wave length, etc.) are to be concurrently controlled in attaining the desired separations[12, 13]

Application of derivative technique of spectrophotometry offers a powerful tool for quantitative analysis of multi-component mixtures. When derivatised, the maxima and minima of the original function take zero values, and the inflections are converted into maxima or minima, respectively. The derivative curves are more structured than the original spectra, thus enabling very tiny differences between the original spectra to be identified. DS method has been widely used to enhance the signal and resolve the overlapped peak-signals due to its advantages in differentiating closely adjacent peaks, and identifying weak peaks obscured by sharp peaks. The main disadvantage of D is its dependence on instrumental parameters like speed of scan and the slit width. The instrumental conditions of recording parent zero-order spectrum have strong influence on the shape and intensity of its derivative generations. In general, DS has been directly used for the simultaneous determination of organic and inorganic compounds. Fig. 1 shows the applications of DS in several areas since last three decades ago. As can be seen from this figure pharmaceutical and inorganic analyses are two areas where DS

has been more used. DS offers greater selectivity than normal spectrophotometry in the simultaneous determination of two or more components without previous chemical separation. Principles, advantages and applications of this technique have been reviewed in four works published some years ago.[14-17]

In these works, we exposed the different aspects of derivative ultraviolet/visible spectrophotometry: theoretical, instrumental devices and analytical applications, the first until 1986, the second until 1993, the third until 2003 and the fourth until 2008. The purpose of this paper is to review the articles on the anterior cited aspects published since 2009, in order to complete the review since our last publication[17, 18]

Quality control on pharmaceutical products is undoubtedly an important and widely debated topic. Hence, in literature, various methods have been proposed to check quality of medicines, either qualitative[19-21] or quantitative[19, 22 23] involving either destructive or non-invasive online techniques. Recently, due to the benefits they bring, several non-destructive methodologies based on spectroscopic techniques (mainly Near-Infrared NIR) combined with chemometric tools have been proposed for pharmaceutical quality check[24-26]

3. QUALITATIVE ANALYSIS

As discussed in the previous section, exploratory analysis is a first and fundamental step in chemometric data processing and, in some cases, it could be the only approach needed to characterize the samples under investigation. However, due to its unsupervised nature, it provides only a (hopefully) unbiased picture of the data distribution but it lacks any possibility of formulating predictions on new observations, which on the other hand may be a fundamental aspect to solve specific issues. In practice, very often quality control and/or authentication of pharmaceutical products rely on some forms of qualitative or quantitative predictions. For instance, the quantification of a specific compound (e.g., an active ingredient or an excipient) contained in a formulation is a routine operation in pharmaceutical laboratories. This goal can be achieved by combining instrumental (e.g. spectroscopic) measurements with chemometric regression approaches [25, 27, 28]

As already introduced in the previous section, in chemometric applications, in general, and in the context of pharmaceutical analysis, in particular, one is often interested in using the

experimentally collected data (e.g., spectroscopic profiles) to predict qualitative or quantitative properties of the samples. While the regression methods for the prediction of quantitative While the regression methods for the prediction of responses have been already presented and discussed in section Regression, the main chemometric approaches for the prediction of qualitative properties of the individuals under investigation are outlined herein. These approaches are generally referred to as classification methods, since any discrete level that the qualitative variable can assume may also be defined as a class (or category)

Chemical information associated with the knowledge of pure spectra or pure concentration profiles can also be introduced in the optimisation as an additional equality constraint[29-31]

The known profiles may be set to be invariant along the iterative process. Following this concept, the knowledge of a profile does not need to be complete to be used. When some elements are known, they can also be fixed.

This has opened the possibility to use two-way resolution methods for quantitative purposes. Thus, some data sets analogous to those used in multivariate calibration, formed by the signals recorded in a series of calibration and unknown samples, can be analysed. The quantitative information is obtained by resolving the system using an additional constraint that fixes the known concentration values of the analyte(s) in the calibration samples in the related concentration profile (s) This approach provides also the qualitative information related to resolution methods in the form of pure signal profiles associated with the analyte and interferents and has proven to be as powerful as classical multivariate methods in examples where the net signal of the analyte is not very minor.

3.1. CHEMOMETRIC METHOD

- **Principal Component Analysis :-**

Principal component analysis (PCA) is a projection method, which looks for directions in the multivariate space progressively providing the best fit of the data distribution, i.e., which best approximate the data in a least squares sense. This explains why PCA is the technique of choice in the majority of cases when exploratory data analysis is the task: indeed, by definition, for any desired number of dimensions (components) F in the final representation, the subspace identified by PCA constitutes the most faithful F-dimensional approximation of the original data. This allows compression of the data dimensionality at the same time reducing to a minimum the loss of information. In particular, starting from a data matrix X(N×M), Principal Component Analysis is based on its bilinear decomposition, which can be mathematically described by Equation (1):

$$\mathbf{X = TP^T + E}$$

Many exploratory procedures are often methods derived from Principal Component Analysis (PCA), one of the most basic and widely used chemometric tools devoted to find the number and direction of the relevant sources of variation in a bilinear data set **.** The information provided by the global and local application of Principal Component Analysis to the data set can be essential in resolution. Thus, the first step in many resolution methods is the determination of the total number of chemical components in the data set and the ambiguity of the final solutions depends basically on the distribution and overlap of these compounds along the data set, i.e. on the local rank information obtained.

PCA can also be used for routine quality checks at the end of a production process. For example, laser-induced breakdown spectroscopy (LIBS) and PCA were combined with the aim of obtaining qualitative information about the composition of different pharmaceuticals.

3.2. PHARMACEUTICAL APPLICATION

The weight of 20 capsules was accurately measured. Subsequently, in a dry, clean mortar, the contents were pulverized. Thereafter, in a 100 ml volumetric flask, a powder weight equivalent to 40 mg of TAM and 50 mg of DUT was separately transferred, and sufficient methanol was used to dissolve it. The solution was shaken for 10 min on a rotatory shaker followed by sonication for 30 min. The obtained solution was subjected to centrifugation at 3000 rpm for 30 min. Finally, it was filtered, and then the final volume was adapted with methanol to obtain a final concentration of 400 lg/mL TAM and 500 lg/Ml DUT. Aliquots from working

solutions were employed for quantification of TAM and DUT in their dosage form by directly implementing the developed method.

An accurately weight amount or volume equivalent to 250 mg of AMP and 16 mg of ETHOP was dissolved to 10-mL methanol and sonicated for 5 min. The solutions were transferred quantitatively to 15-mL volumetric flask, and diluted to the volume with methanol. Then 0.1 mL was transferred into a 100-mL volumetric flask and completed to volume with the same solvent. To get a solution claimed to contain 16.66 µg and 1.06 µg of AMP and ETHOP, respectively. The spectra of the resulting solution were scanned in the range 200-400 nm.

However, PCR and PLS employ latent variables instead of original variables, which might obscure the interpretation of the modelling results. MLR yields simple models that allow us an easier interpretation of the resulting regression. However, when multicollinearity occurs in the data, overfitting problem is encountered and the MLR models give misleading results **96,97** To overcome this problem, the application of MLR models usually requires variable selection for building well-fitted models. Within this scope, the successive projections algorithm (SPA) is one of the most promising methods as a variable selection strategy for MLR, which has the advantage of finding a small representative set of spectral variables with minimum collinearity In addition to providing simpler models, SPA often leads to better prediction results, as compared to full-spectrum calibration methods, which may be attributed to the removal of uninformative variables for the modelling process This method has been successfully employed in several analytical applications over the past 10 years In this context, multivariate calibration methods in combination with derivative spectrophotometry can be used as a highly effective technique for simultaneous determination of components with serious spectral overlapping, because of the potential ability to exploit minor spectral features In this study, the original and first-derivative absorption spectra were used for the simultaneous determination of MP and HQ in their mixtures and in real cosmetic samples, using SPA-MLR. The results obtained by the other multivariate calibration methods (PCR and PLS) were evaluated and compared with SPA-MLR, using the RMSEC, RMSECV and RMSEP values. The SPA-MLR model, using first-derivative absorbance data, was then applied for the simultaneous determination of MP and HQ in several cosmetic samples.

In order to assess the applicability of the proposed methods to the analysis of real samples, they were applied to the determination of these drugs in pharmaceutical formulation. Five replicate measurements were made. The results are shown in Table 8. The good agreement between these results and the label claims indicates the successful applicability of the proposed procedure for the simultaneous determination of paracetamol, ibuprofen and caffeine in real sample. To check the validity of the proposed method, after the addition of the known amounts of PCT, IB and CAF to the commercial formulation, we found that the amount of these drugs did not change. The recovery of each drug was calculated by comparing the concentration obtained from the spiked mixtures with those of the pure drug (standard addition method). These results are shown . Moreover, we compare the spectra obtaining from the mixture of PCT, IB and CAF in standard and drug formulation solutions that showed similar patterns in their spectra (Fig. 4.). These findings indicate that excipients placed in

commercial preparation did not interfere in the measurement of PCT, IB, and CAF in pharmaceutical formulation.

4. QUANTITATIVE ANALYSIS

Chemometrics is applied in areas comprising experimental parameter optimization, data quality improvement, identification and quantification of targeted chemical components, pattern recognition techniques for clustering and classification, multivariate model establishment to correlate chromatographic properties with molecular descriptors and prediction of properties or activities of chemical compounds or technological materials (**quantitative structure-activity or structure property relationships**) to find out hidden relationships existing between the available data and the desired information.

5.1 Quantitative application

Application of the Described Models for Quantitative Analysis of Duodart Capsules :-

The proposed chemometrically assisted UV spectrophotometric method was used and was successful in the quantification of TAM and DUT in Duodart capsules. The results of the developed methods were statistically compared to those acquired by the HPLC reported methods indicating that there are no significant differences, as shown.

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PHARMACEUTICAL APPLICATION OF QUALITATIVE

94. A New Chemometrically Assisted UV Spectrophotometric Method for Simultaneous Determination of Tamsulosin and Dutasteride in Their Pharmaceutical Mixture Khalid A.M. Attia ,1 Ahmed Serag ,1 Sherif M. Eid ,2 and Ahmed Emad F. Abbas **m…**

95. A comparative Study of two analytical techniques for the simultaneous determination of Amprolium HCl and Ethopabate from combined dosage form and in presence of their alkaline degradation Mai A Basha*a, Said A. Hassan b Mohamed K. Abd El-Rahmanb, Lories Bebawya, Azza A.Moustafab **m…**

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