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Chemometrics Approach to Drug Analysis – An Overview

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ABSTRACT

Chemometrics is the use of mathematical and statistical methods to improve the understanding of chemical information and to correlate quality parameters or physical properties to analytical instrument data. It is a data-driven multidisciplinary science that allows maximum collection and extraction of useful information from the analytical data of numerous application areas such as chemistry, biochemistry, medicine, biology and chemical engineering. This review focuses mainly on numerous chemometric models used and their relevant applications in the field of pharmaceutical sciences.

Keywords: Chemometrics, analytical data, multidisciplinary science, pharmaceutical sciences.

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INTRODUCTION

The term “Chemometrics” was coined by Svente Wold in 1972 and is concerned with the application of mathematical and statistical techniques to extract chemical and physical information from complex data with the application of computer science. Various algorithm and analogue ways are available for processing and evaluating the data. They can be promoted to various fields like medicine, pharmacy, food control, environmental monitoring and it is continuing to diverge into new fields such as metabonomics [1, 2]. 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. [3, 4].

DIFFERENT CHEMOMETRICS MODELS FOR ANALYSIS OF DATA:

Chemometrics methods can be categorized in several different ways like clustering, regression and explorative methods. Chemometricians have adopted methods from other research fields such as econometrics and psychometrics where bilinear partial squares and multiway methods, respectively, had been applied and refined. Methods are separated according to how they explore the data arrays and a distinction can be drawn between bilinear, non-linear and multiway methods as well as between projection, latent variable and factor based methods. However, some methods overlap between the above categorizations.

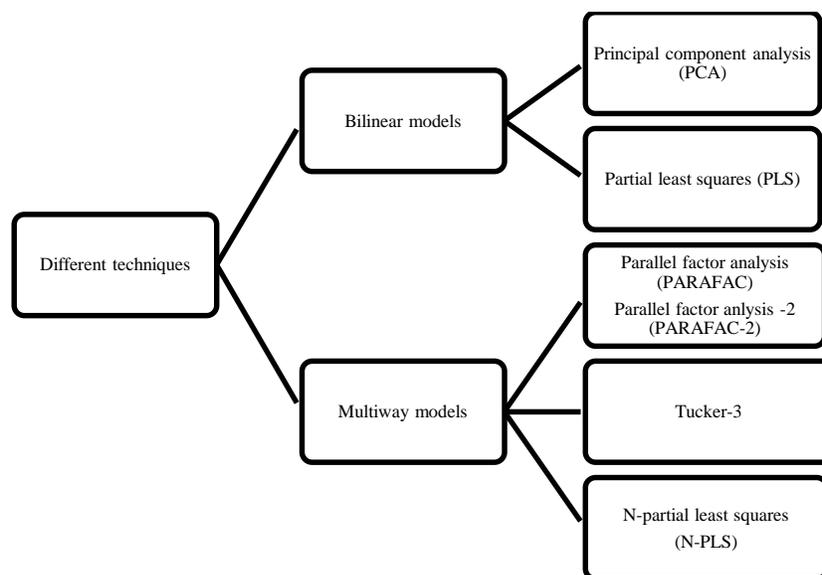


Figure 1: Classification of chemometrics methods

Bilinear model:

Bilinearity means the system is linear with relevance to its decomposition, i.e. the system is linear in its estimated parameters. In bilinear models, the knowledge of data is arranged in data matrices so that each horizontal row contains samples and vertical column has variables. Bilinear chemometric techniques include the following:

Principal Component Analysis (PCA):

This is a simple and non-parametric technique used for extracting the relevant information from the data sets on the basis of their affinity and differences. It is widely used in multivariate data analysis. PCA decreases the dimensionality and multivariate data compression in the fields of science. During process monitoring, it can be used to develop a correlation structure between variables and also to examine the changes. Thus it reduces the number of variables in the process. If for a series of sites, or objects, or persons, a variety of variables are measured, then each variable will have a variance, and usually, the variables will be associated with each other that is, there will be statically variance between pairs of variables. Today, PCA is one of the massive utilized multivariate models because of its wide applicability for multivariate problems [5, 6].

Special cases of PCA:

The most widely used special cases of PCA are principal component regression (PCR), soft independent modelling of class analogy (SIMCA) and multi-way principal component analysis (MPCA).

Principal component regression (PCR) is a regression analysis technique that is based on principal component analysis (PCA). Typically, it considers regressing the outcome (also known as the response or the dependent variable) on a set of covariates (also known as predictors, or explanatory variables, or independent variables) based on a standard linear regression model, but uses PCA for estimating the unknown regression coefficients in the model. In PCR, instead of regressing the dependent variable on the explanatory variables directly, the principal components of the explanatory variables are used as regressors. One major use of PCR lies in overcoming the multicollinearity problem which arises when two or more of the explanatory variables are close to being collinear [7].

Soft independent modelling by class analogy (SIMCA) is a statistical method for supervised classification of data. The method requires a training data set consisting of samples (or objects) with a set of attributes and their class membership. The term soft refers to the fact the classifier can identify samples as belonging to multiple classes and not necessarily producing a classification of samples into non-overlapping classes. SIMCA as a method of classification has gained widespread

use especially in applied statistical fields such as chemometrics and spectroscopic data analysis [8].

Multi-way principal components analysis (MPCA) is an efficient tool for reducing higher dimensional data arrays. MPCA allows the detection of spatial and temporal factors of influence and the classification of the parameters can be considered according to these factors. Rene et al., developed a multi-way principal components analysis for a complex data array resulting from physicochemical characterization of natural waters [9]. Molloy et al., applied a multiway principal component analysis for Identification of process improvements in pharmaceutical manufacture [10].

Luciana et al. applied chemometric tools, such as principal component analysis (PCA), consensus PCA (CPA), to a set of forty natural compounds, acting as NADH-oxidase inhibitors [11].

Partial Least Squares (PLS):

Partial least squares (PLS) are a regression method for multivariate data. It is one of the widely implemented methods which describe the relationship between different sets of different observed variables by the means of latent variables. The basic theory of this method is that it modifies relations between sets of the observed variables by a small number of latent variables (not directly noticed or consistent) by assimilate regression, dimension reduction techniques, and modelling tools [12-16]. The latent variables increase the covariance between the different sets of variables. PLS is identical to canonical correlation analysis (CCA) and can be used as a discrimination tool and dimension reduction method like principal component analysis (PCA). PLS is widely used approach as it can process large chemical data [17-21]. The determination of flow properties of pharmaceutical powders by near infrared spectroscopy (NIR) spectroscopy was done using Partial least square technique by Sarraguca et al [22]. Cordeiro et al. conducted multivariate spectroscopic determination of lamivudine- zidovudine associations by partial least square regression(PLS) [23].

Multi-way models:

Multi-way models are used when the data is multivariate and linear in more than 2 dimensions. These can be considered to devise a model in n-dimensions so that the system is linear in n-dimensions. A three-linear system is often visualized as a data cube and is called a 3-way data or 3-way array whereas the bilinear system is a rectangular matrix that can be considered as 2-way data. The multi-way modelling originated from psychological data treatment where bilinear data analysing methods were not adequate. Multi-way methods are also applied to process control as well as regression analysis. Some of the advantages of multi-way models are that they have been recognized as useful tools for monitoring batch data since they improve the understanding of the

process and summarize its behaviour in a batch wise manner. The methods like multiway principal component analysis (MPCA) and multiway partial least squares (MPLS) improve the process understanding and review its behaviour in a batch-wise manner and are therefore recognized as tools for monitoring batch data. However, if the initial data contains higher amplitude then it becomes difficult for the models to describe the computed data and therefore multi-way methods that work with three-way or the higher arrangement like parallel factor analysis (PARAFAC) and PARAFAC-2, Tucker-3, and N-partial least squares (N-PLS) are the methods of choice [24-28].

Parallel factor analysis (PARAFAC):

Parallel factor analysis (PARAFAC) is a disintegration method used for the modelling of three-way or higher data and is chiefly intended for data having compatible variable profiles within each batch. The history to interpret PARAFAC is as follows. Cattell (1944) reviewed seven principles for the choice of rotation in component analysis and achieved the principle of “Parallel proportional profiles” as the most basic assumption. This assumption means that the two data matrices with the same variables ought to contain the identical components. By using this assumption as a constraint Harshman (1970) projected a new method to analyse two or more data matrices that contain scores for the same person on the same variables and termed the method as PARAFAC [26,28-30]. PARAFAC could be a generalisation of the principal component analysis (PCA) projection method for a multi-way array. The PARAFAC model has a second-order advantage, i.e. it can handle interferences in new samples by fitting the new interferent with an extra component.

Parallel factor analysis-2 (PARAFAC-2):

PARAFAC-2 is also designed for modelling N-way data but, in contrast to PARAFAC, it handles experiments of different lengths and variable profiles that are deviated or in a different phase. It can handle data variable profiles that are deviated or/are in a different phase. In PARAFAC, trilinearity is a basic situation whereas PARAFAC-2 allows trilinearity. However, it is to be noted that PARAFAC may be used for fitting nonlinearity to some extent in one mode only in cases where data shifts from linearity are regular. Both the techniques are mainly applied to inspect chemical evidence from experiments that form a 3-way or higher data structure. For example, chromatographic data, fluorescence spectroscopy, temporal varied spectroscopy data with overlapping spectral profiles, and process data [26, 29, 31, and 32].

Tucker-3:

The Tucker3 method can be used for consolidating and data analysis of the N-way array. The Tucker3 model consists of storing matrices in n modes, factors that are typically rectangular and a

(P, Q, R) dimensional core array G. The Tucker3 core array differs from the PARAFAC core by having at least one off-diagonal core element as non-zero, whereas the PARAFAC has a so-called super-diagonal core array and thus PARAFAC can be expressed as a special case of the Tucker-3 model. This can be used for survey of N-way array data as it consists of N modes of loading matrices. The generalization of the Tucker-3 model, and the fact that it covers the PARAFAC model as a certain case has made it an often used model for decomposition, compression, and interpretation in many applications [26, 29, 33].

N- Partial least squares (N-PLS):

For handling a multiway data extension of PLS method namely N-PLS was made acquainted that uses dependent and independent variables for finding the latent variables for describing maximal covariance. N-PLS decomposition starts by constructing a distinct PARAFAC-like model for dependent response variables and maximize the covariance between the two matrices [25, 29,34].

Kong et al. researched the convergence of triglyceride in people by utilizing fluorescence spectroscopy within the region 220-900nm. Nonlinear partial least squares with cubic B-spline-work based nonlinear change was utilized as the chemometric strategy. Wavelengths within the region of 300-367nm and 386-392nm in the first derivative of the original fluorescence spectrum were the enhanced wavelength combination for the prediction model [35].

APPLICATIONS OF CHEMOMETRICS IN PHARMACEUTICAL FIELD: Chemometrics can be broadly applied to exploratory analysis, regression analysis and classification of data studies. The specific applications of various chemometric models in pharmaceutical field are as follows.

Diagnosis and drug synthesis:

- Diagnosis and detection of significant change in patient's condition during medical treatment and clinical care, prediction of the future medical state of the patient.
- Quality control of laboratory results, standardization and interpretation of laboratory tests in disease monitoring
- Drug synthesis, development and design, tools for drug discovery, SAR, drug mechanism, metabolomics, and proteochemometrics.

Powder flow properties:

To conclude the pharmaceutical properties such as mean particle size, angle of repose, tablet porosity, and tablet hardness. NIR spectra of the Antipyrine granules were measured. This was analysed by principal component regression analysis. With the increase in the water amount, the mean particle size of the granules was found to increase from 81µm to 650µm, and it was possible

to make larger spherical granules with small particle size distribution using a high-speed mixer [36].

Water content determination in excipients: Water content of hygroscopic pharmaceutical excipients largely affects the manufacturing processes and the performance of the final product. The water content of commonly used tablet disintegrants namely crospovidone, croscarmellose sodium and sodium starch glycolate was studied by Szakonyi *et al.*, by simple linear regression [37].

Dissolution studies: Ana Rita explored the application of near-infrared spectroscopy and multivariate data analysis to monitor in-situ and in real-time dissolution tests of an immediate release formulation containing folic acid and four excipients [38].

Tablet-parametric method: Chen *et al.*, predicted the drug content and hardness of intact tablets of theophylline using artificial neural network and near-infrared spectroscopy [39]. Tanabe *et al.* employed NIR spectroscopic methods in combination with principal component regression (PCR) analysis for predicting hardness of the tablet formulations consisting of berberine chloride, lactose, and potato starch. The reflectance NIR spectra of various compressed tablets were used as a calibration set to establish a calibration model to calculate tablet hardness where in the predicted and the actual hardness values exhibited a straight line, an r^2 of 0.925 [40].

Formulation development: Formulation and assessment of protein-loaded solid dispersions by non-destructive methods like powder X-ray diffraction (PXRD), near infrared chemical imaging (NIR-CI) were performed in combination with principal component analysis and partial least square regression [39].

Salt and polymorph screening: Svensson demonstrated that mixtures of polymorphs of carbamazepine can be detected with PCA score plots and that multivariate regression methods, such as PLS, can be used to estimate and determine the composition of these mixtures [41].

Pharmaceutical analysis: Various chemometric methods in combination with UV-Visible spectrophotometry, NIR spectroscopy, fluorescence spectroscopy, electroanalysis, chromatographic separation, and flow-injection analysis for the analysis of drugs in pharmaceutical preparations have been reported.

Chemometrics is of great industrial importance in various chromatographic research areas as a lot of experimental work should be carried out with respect to optimization of different columns, test compounds, mobile phases and their pH, flow rate and peak shape parameters. The chromatographic techniques coupled with chemometric tools provide useful information on separation and elution time. The validation parameters like robustness and ruggedness are also best

evaluated with the help of chemometrics. For binary mixture analysis HPLC is combined with different calibrating techniques like PLS, PCR, CLS, and so forth; hence, they are collectively called HPLC-CLS, HPLC-PCR, and HPLC-PLS. Several liquid chromatographic methods in combination with chemometrics have been applied and reported in various method optimization and validation studies in diversified research areas.

Simultaneous determination of ambroxol hydrochloride and guaifenesin was carried out by HPLC, using principle component regression (PCR), and partial least squares (PLS) [42]. Lan Luan et al. developed HPLC and chemometrics for the quality consistency evaluation of Shuanghuanglian injection [43]. Ghada et al. developed HPLC and chemometrics-assisted UV-spectroscopy method for the simultaneous determination of ambroxol and doxycycline in capsule [44]. HPLC and chemometric methods were used for the simultaneous determination of cyproheptadine hydrochloride, multivitamins and sorbic acid by Gindy et al [45]. Fangliang et al developed a HPLC-DAD method combined with multicomponent chemometrics and antioxidant capacity to monitor the quality consistency of compound bismuth aluminate tablets by comprehensive quantified fingerprint method [46]. Quality evaluation of *Potentilla fruticosa* L. was performed by Wei Liu et al. using high performance liquid chromatography fingerprinting associated with chemometric methods [47]. Chemometrics was also used for development and validation of a RP-HPLC method for simultaneous determination of haloperidol and related compounds by Petkovska et al [48]. A bioanalytical liquid chromatography method for estimation of rosuvastatin calcium in rat plasma samples was developed and validated by Sarwar et al. using chemometric techniques [49]. Cellina et al. performed and reported a novel dispersive liquid-liquid microextraction-HPLC method for gliclazide, glibenclamide and glimepiride quantitation in serum samples where in the method optimization and validation was assisted with chemometrics [50].

Chemometrics has also been widely used in combination with various spectroscopic techniques for the analysis of active molecules in dosage forms, plant materials and biological samples. Chemometrics- assisted simple UV- spectroscopic determination of Carbamazepine in human serum was reported by Camara et al and the results were compared with reference methods [51]. Bhaskar et al. described UV-spectrophotometric assisted chemometric methods for the simultaneous determination of Metformin hydrochloride and Gliclazide in pharmaceutical formulations [52]. Qi et al. performed the characterization of *Gentiana rigescens* using UV and Infrared spectroscopies combined with chemometrics [53].

In metabolomics: Further multivariate chemometrics has been used in metabolomics (study of small molecule metabolite profiles) along with GC/MS and NMR techniques to characterize the

metabolic profiles of biofluids, understand the mechanism of pathogenesis and uncover potential biomarkers of disease progression [2].

Recently chemometrics is also used in toxicity assessment and prediction. It plays an important role in expert systems for toxicity classification, in identification of drugs and toxic substances in complex mixtures and in forensic chemistry [2].

Further chemometrics can also be applied to the study of bioactive compounds in food [2].

Some available chemometric software's: WINSI, NSAS, Vision, Sesame, SpectroMatrix, Anatec, Delight, GRAMS 386, Unscrambler, MatLab, Pirouette.

CONCLUSION:

Chemometrics is the data-driven multidisciplinary science using methods frequently employed in core data-analytic disciplines such as multivariate statistics, applied mathematics, and computer science, in order to address problems in chemistry, biochemistry, medical and pharmaceutical fields, biology and chemical engineering. Different chemometrics models have been applied for the analysis of data of a particular manufacturing process, quality control test, or an instrumental output data with an aim to achieve maximum accuracy, precision, and robustness in a variety of matrices. There is a huge potential for chemometrics in modern analytical and process chemistry as it provides accurate results in a simple and rapid manner. Applications, new methodology and software must go hand in hand for quality products in chemometrics.

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