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A Review on Chemometrics in Pharmaceutical Analysis

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Abstract: ***Chemometrics is a science which involves the application of statistical and mathematical methods to the analytical data for the collection and extraction of information which is useful for analyzing the results. Chemometrics is an essential tool for multivariate data collection and analysis protocols, calibration, process modelling, pattern recognition and classification, signal correction and compression, and statistical process control. It involves various chemometric techniques like bilinear and multivariate models by using spectroscopic, chromatographic and electrochemical methods which helps in the identification and quantitative analysis of active substances in complex mixtures. This review describes various chemometric methods which is mainly applicable for interpretation of UV/Visible spectra, and also the data obtained by other instrumental methods including near infrared (NIR), attenuated total reflectance Fourier transform infrared (ATR-FTIR), terahertz pulse spectroscopy, fluorescence spectroscopy, electroanalysis, high-performance liquid chromatography (HPLC), and flow-injection analysis for the analysis of drugs in pharmaceutical preparations.***

Keywords: Chemometrics, bilinear model, multiway model, spectroscopy, chromatography, pharmaceutical analysis

1. Introduction

Chemometrics is an umbrella term used for a set of mathematical techniques which are applied to the information. The term ‘‘kemometri’’ (‘‘chemometrics’’ in English) was coined by Svante Wold in 1972 by combining the words kemo for chemistry and metri for measure [1]. The journal Chemometrics and Intelligent Laboratory Systems defines chemometrics as ‘‘the chemical discipline that uses mathematical and statistical methods to design or select optimal procedures and experiments, and provide maximum chemical information by analyzing chemical data’’ [2]. By using chemometrics, both predictive and descriptive issues can be solved. The predictive issues include system properties that utilize an elaborated model with the intent of predicting the target properties, desired features. The descriptive issues include properties of the investigated systems that are modeled to learn the relationships and the system structure, which helps in model identification, composition, and understanding. Chemometric methods are versatile and there is a high level of abstraction as it characterizes the scientific disciplines extensively by the application of the statistical and mathematical methods, mainly the multivariate methods. There are various algorithms and analogous ways for processing and evaluating the data and they can be implemented to various fields, namely, medicine, pharmacy, food control, and environmental monitoring [3]. The various Chemometric models for analysis are the following:

1) **Bilinear models**
   - Principal Component Analysis (PCA)
   - Partial Least Squares (PLS)
2) **Multiway models**
   - Classical Least Squares (CLS)
   - Inverse Least Squares (ILS)
   - Parallel Factor Analysis (PARAFAC)
   - Parallel Factor Analysis-2 (PARAFAC-2)
   - Tucker-3 model
   - N-Partial Least Squares (N-PLS)
   - Locally Weighed Regression (LWR)

1) Bilinear models

In this model, the data will be arranged in data matrices so that each vertical column will have variables and each horizontal row has samples [4]. Bilinear models are further categorized as below:

a) Principal Component Analysis (PCA)

PCA is a simple, nonparametric method used for obtaining information from datasets, identifying patterns in data, and expressing the data in a way to highlight their similarities and differences. When applied, it reduces the dimensionality and multivariate data compression exploration in different fields of sciences. It is the most frequently used multivariate methods due to its wide applications in solving the multivariate problems. PCA is used to develop correlation structure of variables and to examine their changes in variable correlations in process monitoring, thus reducing the number of variables in a process. In PCA, the data will be transformed to describe the same amount of variability. Luciana et al. [5] applied chemometric methods, such as principal component analysis (PCA), consensus PCA (CPCA), to forty natural compounds, acting as NADH-oxidase inhibitors. Special cases for PCA are as follows:

- *Principal Component Regression (PCR)* - It is a regression type of PCA where it uses the scores of the PCA model to correlate.
- *Soft Independent Modelling of Class Analogy (SIMCA)* - It is a clustering model involving constructing of separate PCA models for a prior determined class of data which operates on the residual matrix.
- *Multi-way Principal Component Analysis (MPCA)* - It operates with high dimensional data-array by unfolding it prior to bi-linear PCA.

b) Partial Least Squares (PLS)

PLS is widely accepted method which is used for modelling the relationship between different sets of observed variables by the means of latent variables. Wold and co-workers [6] developed projections of the observed data to its latent structure by applying PLS. The basic assumption of this method is that it modifies the relationship between the sets of the observed variables by a small number of latent variables (not directly observed or measured) by using regression, dimension reduction techniques, and modelling tools. In general, the latent variables increase the covariance between different sets of variables. Being similar to canonical correlation analysis (CCA), PLS can be used as a discrimination tool and dimension reduction method as in principal component analysis (PCA) [7]. It can be related to other regression methods like principal component regression (PCR), ridge regression (RR), and multiple linear regression (MLR) where all these methods can be grouped under a unifying approach called continuum regression (CR) [8]. The PLS method is widely applicable in the field of chemometrics as it can process large chemical data. Determination of flow properties of pharmaceutical powders by near infrared spectroscopy NIR spectroscopy was done using Partial least square technique [9]. Due to the presence of substantial nonlinearity, PLS can produce large prediction errors where nonlinear calibration techniques such as nonlinear partial least squares (NPLS), locally weighted regression (LWR), alternating conditional expectations (ACE), and artificial neural networks (ANN) can be applied.

2) Multiway models

Multiway models are used when the data is multivariate and linear in more than two dimension arrays and is more acceptable model for data analyses as bilinear methods cannot provide sufficient results. Generally, univariate measurement is highly sensitive to interferences and it is impossible to differentiate an analyte-specific signal from an interferent in a data spectrum which can be overcomed by multi-way models. This method implies the use of the multiple variables (e.g., the response at a range of potentials or wavelengths, or over the entire range collected to calculate concentrations). These multiway models are applicable for extracting chemical information from spectra due to the ability to determine the compound composition of a mixture along with enhancing chemical understanding and evaluating the relative concentrations of the compounds in a sample. The methods like multiway principal component analysis (MPCA) and multiway partial least squares (MPLS) are used for monitoring the batch data. But, if the original data contains higher dimensions, it becomes difficult to interpret the computed data if the original data contains higher dimensions, so multiway models that work with three-way or higher arrays like parallel factor analysis (PARAFAC and PARAFAC-2), Tucker-3, and N-partial least squares (N-PLS) are used [10].

a) Classical Least Squares (CLS)

CLS involves application of multiple linear regression (MLR) to the classical expression of the Beer-Lambert law of spectroscopy:

$$A=KC \text{ (or } dA/d\lambda=KC)$$

where the matrixes A and $dA/d\lambda$ represent the zero-order absorbance and derivative absorbance matrixes, respectively; C is the concentration matrix; and K is the calibration coefficient matrix [11].

This technique can be applied only to the systems where every constituent in the sample is known. This model cannot predict the constituent concentrations accurately when there is possibility of contaminants in the unknown sample that were not present in the calibration mixtures.

b) Inverse Least Squares (ILS)

ILS also known as P-matrix calibration because it involves the application of multiple linear regression (MLR) to the inverse expression of the Beer-Lambert law of spectroscopy:

$$C=PA \text{ (or } C=P\times dA/d\lambda)$$

where the matrixes A and $dA/d\lambda$ represent the zero-order absorbance and derivative absorbance matrixes, respectively; C is the concentration matrix; and P is the calibration coefficient matrix [11].

This method is suitable to more complex types of analyses which cannot be handled by CLS. Disadvantages of the ILS method are that selection of wavelength can be difficult and time-consuming, and the number of wavelengths used in the model is limited by the number of calibration samples, and it requires large number of samples for accurate calibration.

c) Parallel Factor Analysis (PARAFAC)

Parallel factor analysis (PARAFAC) is a type of decomposition method for modelling three-way or higher data which is mainly applied for the data having congruent variable profiles within each batch. Cattell (1944) reviewed seven principles for the choice of rotation in component analysis and advocated the principle of "parallel proportional profiles" as the fundamental principle. This principle states that the two data matrices with the same variables should contain the same components. Using this principle as a constraint, Harshman (1970) proposed a new method to analyze two or more data matrices which contain scores for the same person on the same variables and termed it as PARAFAC [12].

d) Parallel Factor Analysis-2 (PARAFAC-2)

PARAFAC-2 handles data with different temporal durations and variable profiles that are shifted in a different phase and trilinearity is not so considered. PARAFAC and PARAFAC-2 has been applied for analyzing chemical data from experiments that form a 3-way or higher data structure, for example, chromatographic data, fluorescence spectroscopy measurements, temporal varied spectroscopy data with overlapping spectral profiles and process data [13].

e) Tucker-3 model

Tucker-3 method is used for compression and data exploration of N-way array as it consists of loading of matrices in n modes. The model name is taken from the psychometrician Ledyard R. Tucker who proposed the model in 1966. He proposed a way to calculate the parameters of the model. This model remained as a strong tool for analysis of three-way (and higher-way) data arrays.

f) N-Partial Least Square (N-PLS)

N-PLS method was introduced to handle multiway data extension of PLS method that uses dependent and

independent variables to find the latent variables for describing maximal covariance. N-PLS decomposition occurs by constructing a distinct PARAFAC-like model for dependent response variables and maximizing the covariance between the two matrices [14].

g) Locally Weighted Regression (LWR)

LWR method applies PCR or PLS combining with a weighting scheme so that calibration samples which are closest to the sample to be predicted are given higher weight. There may be possibility of many variants and the preferred variant should be the one that has PLS for all the samples with equal weights. Hence, when the data are linear and not clustered, the local method becomes a global method. LWR was shown to perform well during analyzing clustered or nonlinear data, but not studied to the same extent as the preceding methods, so lesser diagnostics are available and is less preferred. This method is more time-consuming than other methods, because it requires several sets of latent variables to be determined and also less robust towards wavelength shift than other methods.

2. Applications of Chemometrics in Pharmaceutical Analysis

1) UV-Visible Spectrophotometry

UV-Visible spectrophotometry is a rapid, inexpensive analytical technique and it is highly suitable for analyzing the pharmaceutical preparations containing components that absorb in the UV region. The lack of specificity of UV-Vis absorption hinders its application in the presence of overlap between bands of different components. The development of MLR and factor-based techniques has enabled the application of UV-Vis spectrophotometry for analyzing complex mixtures without the need for a prior separation. Table 1 [15-45] illustrates some of the applications of chemometrics to UV-Visible spectrophotometry which are successfully applied for pharmaceutical analysis.

2) Near Infrared Spectroscopy (NIRS)

The NIRS range is between 780 and 2500 nm where transition occurs from visible spectral range to the mid-IR region. In the NIR region (800–2500 nm, or 12821–4000 cm^{-1}), mainly vibrations of –CH, –OH, –SH, and –NH bonds are generally observed. All the absorption bands are obtained as a result of overtones or combinations of the fundamental mid-IR bands. It is a fast, nondestructive and noninvasive analytical method where it requires lesser quantity of sample for analysis. Associated with chemometrics, it becomes a powerful tool for the pharmaceutical industry for analysis of solid, liquid and biotechnological pharmaceutical forms. It is also used for the determination of nonchemical properties (density, viscosity) of the sample [46]. Different fundamental vibrations can be described using a harmonic oscillator model with different energy and space levels. In NIR spectroscopy, various radiation sources are selected and the spectra of unknown sample are being recorded by different detectors at a particular wavelength. Depending on the wavelength selection, the spectrophotometers used in NIRS are of two types, that is, discrete wavelength and whole spectrum. In discrete wavelength, light sources filters like LEDs are used to get narrow bands while whole spectrum involves diffraction grating. The analytical information from the NIR spectra can be extracted by using multivariate analysis technique [47]. NIRS can also be used with other calibration models like PLS and PCR. Tomuta et al. applied NIR chemometric method for assay of meloxicam from powder blends for tableting using partial least square regression (PLS) and principal component regression (PCR) methods [48]. Awaa et al. studied the comparision of two pharmaceutical tablets of pentoxifylline (PTX) and palmitic acid with NIR spectroscopy and chemometrics self-modelling curve resolution (SMCR) analysis which gave an idea about the qualitative and quantitative information [49].The pharmaceutical applications of NIRS and chemometrics are classified into two classes: qualitative analysis and classifications, and quantitative applications [50].

(a) Qualitative analyses, identification, and classifications:

Qualitative analysis involves classification of samples according to their NIR spectra. NIR spectral identifications are based on pattern recognition methods. It is applicable in pattern recognition methodologies within chemistry, biology, and food sciences. The classification techniques can be divided into two categories: unsupervised and supervised. In the unsupervised classification, samples are classified without prior knowledge, except the spectra. For supervised pattern recognition a prior knowledge, i.e., the category membership of samples, is required. Then the model performance is evaluated by comparing the classification predictions to the true categories of the validation samples. The pharmaceutical applications in the field of qualitative analyses can be presented as follows:

- Analysis of starting materials: The identification of raw materials is now a common NIRS application due to the minimal sample preparation. NIRS can be applied to control excipients, active pharmaceutical ingredients (APIs), and final products. Ulmschneider et al. [51] applied NIRS to identify different types of starches, sugars, celluloses, intermediates, and active ingredients with PCA and the cluster calibration module of Nircal® software (Büchi AG, Switzerland). Cellulose ethers were identified by NIRS. Different types of polyvinylpyrrolidones (povidones) are characterized by their viscosity measured in water. Kreft et al. [52] developed an NIRS method using soft independent modeling of class analogy for the determination of the povidone types. The identification of raw material can be performed directly upon reception in the warehouse or during the dispensing.
- Tablets: A method was developed for the identification of illegal ecstasy tablets [53]. The main identified substances were N-methyl-3,4-methylendioxyamphetamine, N-ethyl-3,4-methylendioxyamphetamine, and amphetamine where discrimination of the substances in tablet matrixes was possible. Transmission NIRS combined with chemometric methods can be applied for identity confirmation of clinical trial tablets.

(b) Quantitative Analyses of Pharmaceutical Preparations

It is applicable in determination of chemical compound content such as APIs, excipients, or moisture in pharmaceuticals. Samples can be of various types, e.g.,

powders, granules, tablets, liquids, gels, films, or lyophilized vials. A study has shown the determination of ethanol, propylene glycol and water directly through amber plastic bottle. NIRS is used for the quantitative determination of APIs, excipients, moisture, or coating thickness. NIRS, in combination with PLS-1, was used for the simultaneous determination of the active principles. Table 2 illustrates some of the applications of NIRS in the analysis of pharmaceutical compounds [54-65].

3) Attenuated Total Reflectance Fourier Transform Infrared (ATR-FTIR) Spectroscopy.

ATR-FTIR spectroscopy is based on curvature of light beams passing through different media and also depends on the molecular vibration. Transmitting radiations, like UV, IR, and visible, are used to produce the ATIR spectrum.. These radiations are made to pass through the sample which is situated in an optical crystal to determine the incident radiation attenuated by the sample. ATR spectrometry is used in laboratory testing, medical diagnostics, and clinical assays. ATR gives reliable spectrum for semisolid, murky, turbid, and optically dense solutions. ATR in combination with IR spectroscopy can be used for the characterization of the solid states. ATR crystal is coated with Zn-Se crystal allows the IR radiation to pass through aqueous solution [66]. ATR-FTIR spectroscopy is used for surface analysis of the sample and requires less amount of sample. The powder samples have to be compressed on the ATR crystal to obtain reproducible and good quality spectra. In ATR spectroscopy, when incident light falls on crystal only an evanescent wave can pass into the sample. Szakonyi and Zelko et al. [67] study the water contents of superdisintegrant pharmaceutical excipients by ATR-FTIR spectroscopy using simple linear regression. In this water content is determined for three common superdisintegrants (crospovidone, croscarmellose sodium, and sodium starch glycolate). Water spectra were observed in between 3700 and 2800 cm^{-1} and other spectra were observed due to compaction of the samples on ATR crystal by using small pressure IR range in between 1510 and 1050 cm^{-1} and calibration curve was made in between these ranges. Baseline correction is done to maintain the linearity of the calibration curve. Chemometric methods like simple regression could be employed for the detection of water content of the powdered hygroscopic materials.

4) Terahertz Pulse Spectroscopy

The terahertz pulse spectroscopy range is between 10 and 330 cm^{-1} and 300 GHz and 10 THz. It is a nondestructive method used for the analysis of polymorphic forms and crystalline state of active pharmaceutical ingredients. The terahertz radiation can pass deep enough through the packaging material as well as the container. Based on the principle of the Auston switch [68], terahertz pulse spectrometer uses coherent generation and detection of fem to second THz pulse. In descriptive applications, properties of chemical systems are modelled for understanding the relationships and structure of the system. In predictive applications, properties of chemical systems are modelled with the prediction of new properties or behaviour of the system. Chemometrics has been used for the determination of different pharmaceutical properties of powders, granules, and tablets as it provides an ideal method of extracting quantitative information from samples. An efficient method was developed for the quantitative chemical imaging using terahertz pulse spectroscopy where partial least square type 2 regression was applied [69].

5) Fluorescence Spectroscopy

Fluorescence spectroscopy is widely used in quantitative analysis because of its high sensitivity and selectivity as well as its relatively low cost. This technique has not been widely applied to the simultaneous direct estimation of several fluorescent components in mixtures, because the fluorescence spectra of individual substances contain broad bands that often overlap. Several methods have been proposed to resolve such problems without manipulation of the samples or using time-consuming and highly expensive separation techniques. Due to the ability of chemometric methods to resolve the complex systems, Table 3 illustrates the application of chemometrics and fluorescence spectroscopy for analysis of pharmaceuticals [70-80].

6) HPLC (High-Performance Liquid Chromatography)

HPLC method is used for the analysis of multicomponent pharmaceutical formulation. In HPLC, various kinds of injection and selective treatments are used for the analysis of samples. Different conditions like selection of the column, selection of various mobile phases with various compositions, temperature of the column, were optimized and selection of one specific wavelength has to be done for accurate analysis of results. HPLC is a very sensitive analytical technique for determination in which some factors like error in linear regression, error in chromatographic area, and fluctuation during single wavelength detector response could affect the outcome of results. According to the chemometric method, HPLC uses a PDA detector for the binary mixture analysis and it is combined with different calibrating techniques like PLS, PCR, CLS hence, they are collectively called HPLC-CLS, HPLC-PCR, and HPLC-PLS. For the statistical comparison, various tests are involved like the t-test, ANOVA test, and F test. Evaluation of the response from detector is based on the function of the peak area. Dinc¸ et al. [81] studied chemometric determination by high-performance liquid chromatography (HPLC) with photodiode array (PDA) detection and implemented for simultaneous determination of naproxen sodium and pseudoephedrine hydrochloride in tablets. The experimental results obtained from HPLC-chemometric calibrations were compared with those obtained by a classic HPLC method. Abdelkawy et al. carried out simultaneous determination of a mixture of ambroxol and guaifenesin in cough cold formulation by HPLC and multivariate calibration methods. The combinations of HPLC with a chemometric technique are as follows.

- *HPLC-CLS Approach:* This approach is based on the application of the multilinear regression (MLR) to ratio the peak of individual drugs. In this approach, the matrix equation is applied.
- *HPLC-PCR Approach:* In this approach reprocessing of the ratio of drug concentration and peak area of the individual drug was done by mean centering as Ro and Co. Investigation was done on the covariance dispersion matrix of the centered matrix Ro. Normalized eigenvalues and eigenvectors can be extracted from a square covariance matrix. The highest value of eigenvalues helps in obtaining the number of optimal

principal components (eigenvector (P)). Other eigenvalues and eigenvectors are ignored. Coefficient b is determined by $b = P \times q$, where P is matrix of the eigenvector and q is the C-loading given by $q = D \times TT \times$Ro. TT represents the transpose score matrix. T and D is a diagonal matrix having components inverse to selected values. Drug content was calculated by Cprediction $= b \times R$sample. For data treatment PLS toolbox 3.5 in MATLAB 7.0 software could be used.

- HPLC-PLS Approach: The orthogonalized PLS algorithm involves, simultaneously, independent and dependent variables on the data compression and decomposition operations for PLS calibration. To obtain the decomposition of both concentration and ratio of peaks area matrix into latent variables HPLC- PLS calibration method in HPLC data, $R = T \times PT + E$ and $C = U \times QT + F$ was used. The linear regression equation Cprediction $= b \times R$sample was used for estimation of drug in the samples. Vector b was given as $b = W \times (PT \times W) - 1 \times Q$, where W represents a weight matrix. Application of this method was done using PLS toolbox 3.5 in MATLAB 7.0 software [82].

7) Electroanalysis

The electroanalytical methods along with the application of chemometrics are used for simultaneous quantitative prediction of analytes or qualitative resolution of complex overlapping responses. Typical methods include PLS, ANNs, and multiple curve resolution methods. Many electrochemical methods, especially voltammetric and polarographic techniques, have been described for application in analysis of pharmaceuticals and related materials. Pharmaceutical preparations are complex, often consisting of several drugs mixed in different benign matrixes, thus the response profiles from voltammetric and polarographic measurements often consist of many overlapping signals. The use of chemometrics is essential in order to resolve the composite signals and facilitate the prediction of the component drugs in a preparation. Table 4 illustrates some of the applications of chemometrics in electroanalysis [83-89].

8) Flow-Injection Analysis

Flow-injection analysis (FIA) and related flow techniques in combination with chemometric methods can be used to perform multicomponent determinations of drugs. Flow systems contribute to achieve high sample throughput, and minimize sample and reagent consumption in automated, simple, miniaturized procedures. Selectivity for each analyte of interest depends on physicochemical approaches (e.g., specific reagents, multiparametric detection devices, and multichannel setup). But the performance of these strategies is limited, and interference problems may sometimes arise. In these circumstances, chemometric methods for data analysis can be exploited to attain selectivity. In this way, FIA methods can be extended to complex matrixes from pharmaceutical, clinical, and food fields. Table 5 summarizes some applications involving the combination of FIA and chemometric methods for analysis of multicomponent drug mixtures [90-95].

3. Conclusion

Chemometrics and its methods 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. It has wide applications in pharmaceutical and medical field. There is a high level of abstraction as it characterizes the scientific disciplines extensively by the application of the statistical and mathematical methods. The chemometric methods are expected to provide a rapid quantitative analysis of pharmaceutical properties of intermediate and finished dosage forms as characterized by the simple, nondestructive, and highly sensitive nature of the method. Chemometrics has advanced in parallel with advancing analytical instrumentation and computational capability. Pharmaceutical industrial viability of chemometric techniques could range from setting quality control specifications for raw material, powders, and dosage forms to control of various manufacturing processes and steps. The implementation of chemometric techniques with a view of ensuring overall production process control entails the use of analytical techniques capable of providing accurate results in a simple and rapid manner.

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Table 1: Applications of chemometrics to UV-Visible spectrophotometry

Analyte	Sample form	Regression method
Telmisartan and hydrochlorothiazide	Tablet	PLS-1 and PCR [15]
Ezetimibe and simvastatin	Tablet	CLS [16]
Amoxicillin trihydrate and sodium diclofenac	Tablet	PLS-1 [17]
Triamterene and xipamide	Tablet	CLS, PCR, PLS [18]
Tazarotene	Gel	PCR, PLS [19]
Pyridoxine hydrochloride and isoniazid	Tablet	PCR, PLS [20]
Dienogest and estradiol valerate	Tablet	PCR, PLS [21]
Drotaverine hydrochloride, caffeine, and paracetamol	Tablets	PCR, PLS-1 [22]
Acetaminophen and ascorbic acid	Pharmaceutical products, human serum, and urine	PCR, PLS [23]
Metformin, pioglitazone, and pioglitazone acid degradate	Tablets	CLS, PCR, and PLS-2 [24]
Pyritinol dihydrochloride	Tablets	CLS, PCR, and PLS [25]
Oxybutynin hydrochloride	Tablets and syrup	PCR, PLS [26]
Chlorpheniramine maleate enantiomers	Enantiomers	PLS [27]
Nebivolol and hydrochlorothiazide	Tablets	PCR, PLS [28]
Diflunisal and naproxen	Tablets and suppositories	CLS, PLS-1, and PCR [29]
Rabeprazole	Tablet	CLS, PLS, and PCR [30]
Clopidogrel bisulfate and aspirin	Tablets	ILS, CLS [31]
Nifuroxazide and drotaverine hydrochloride	Capsules	CLS, PLS, and PCR [32]
Norfloxacin and tinidazole erythromycin and trimethoprim	Tablets and oral suspension	CLS and PCR [33]
Bisacodyl in the presence of its degradation products	Tablets and suppositories	CLS, PLS, and PCR [34]
Naproxen sodium and pseudoephedrine hydrochloride	Tablets	CLS, PLS, and PCR [35]
Caffeine, 8-chlorotheophylline, and chlorphenoxamine hydrochloride	Tablets and suppositories	PLS and PCR [36]
Theophylline	Syrup	PLS [37]
Chlorpheniramine maleate, phenylpropanolamine hydrochloride, and propyphenazone	Tablets and capsules	PCR and PLS-1 [38]
Dextromethorphane hydrobromide, phenylephrine hydrochloride, chlorpheniramine maleate, methylparaben, propylparaben, ephedrine hydrochloride, and benzoic acid	Syrup	PCR and PLS-1 [39]
Atenolol, amiloride hydrochloride, and chlorthalidone	Tablets	PCR and PLS-1 [40]
Trimethoprim combined with sulfamethoxazole or sulfamethazine or sulfafurazole	Tablets	PLS [41]
Cyproheptadine hydrochloride, thiamine hydrochloride, riboflavin- 5-phosphate sodium dihydrate, nicotinamide, pyridoxine hydrochloride, and sorbic acid	Syrup	PCR and PLS-1 [42]
Cilazapril and hydrochlorothiazide	Tablets	CLS, ILS, PCR, and PLS-1 [43]
Mefenamic acid and paracetamol	Tablets	CLS, ILS, PCR [44]
Metamizol, acetaminophen, and caffeine	Tablets	ILS, PCA [45]

Table 2: Applications of NIRS in the analysis of pharmaceutical compounds

Analyte	Sample form	Regression method
Acetaminophen	Syrup	PLS [54]
Acetaminophen and caffeine anhydrate	Tablets	PLS [55]
Chlorogenic acid, caffeic acid, luteoloside, baicalin, ursodesoxycholic acid, and chenodeoxycholic acid	Injection	PLS [56]
Rifampicin, isoniazide, and pyrazinamide	Tablets	PLS [57]
Ticlopidine hydrochloride	Tablets	PLS [58]
Cefoperazone sodium	Raw material	PLS [59]
Testosterone	Thin-film composites	PCR [60]
Vitamin C	Food and pharmaceutical products	PLS [61]
Oxytetracycline	Oxytetracycline base	PLS, PCR [62]
Clotrimazole	Extruded film	PLS [63]
Metformin, Ibuprofen	Tablets	PLS [64]
Dexeketoprofen	Hydrogel	PLS [65]

Table 3: Application of chemometrics and fluorescence spectroscopy for analysis of pharmaceuticals

Analyte	Sample form	Regression method
Pyridoxine and melatonin	Tablets	PCR and PLS [70]
Propranolol, dipyridamole, and amiloride	Tablets	PARAFAC [71]
Naproxen, salicylic acid, and acetylsalicylic acid	Pharmaceuticals and human plasma	PLS [72]
Salicylic acid, codeine, and pyridoxine	Tablets and capsules	PLS [73]
Nalidixic acid and 7-hydroxymethylnalidixic acid	Urine samples	PCR and PLS [74]
Acetylsalicylic acid, codeine, and ephedrine	Urine samples	PLS [75]
Norfloxacin, ofloxacin, and enoxacin	Urine samples	PLS [76]
Furosemide and triamterene	Urine samples	PLS [77]

Nafcillin and methicillin	Synthetic mixtures	PLS [78]
Salicylic acid and diflunisal	Human serum	PLS [79]
Galantamine	Artificial and natural water samples	PARAFAC [80]

Table 4: Applications of chemometrics in electroanalysis

Analyte	Sample form	Regression method
Isoniazid and rifampicin	Human serum	PLS [83]
Epinephrine and norepinephrine	Biological samples	PCR [84]
Dopamine and ascorbic acid	Human serum	CLS, PCR, and PLS [85]
Enrofloxacin and ciprofloxacin	Urine and capsules	PCR [86]
Paracetamol and phenobarbital	Tablets	PCR and PLS [87]
Chlorpromazine and promethazine hydrochloride	Rabbit blood	PCR and PLS [88]
Rabeprazole sodium	Tablets	CLS, PCR, and PLS [89]

Table 5: Applications involving the combination of FIA and chemometric methods for analysis of multicomponent drug mixtures

Analyte	Sample form	Regression method
Levodopa and benserazide	Tablets	Multiway PLS PARAFAC [90]
Levodopa and carbidopa	Tablets	PLS [91]
Ofloxacin and ciprofloxacin Ofloxacin and norfloxacin	Pills	PLS [92]
Morphine and naloxone	Synthetic drug mixtures	MLR, PLS [93]
Codeine and noscapine	Syrups	PLS, multiway PLS [94]
Ciprofloxacin, norfloxacin, and ofloxacin	Human urine	Unfolded PLS, multiway PLS, PARAFAC [95]