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Review:

Chemometrics-Assisted UV-Vis Spectrophotometry for Quality Control of Pharmaceuticals: A Review

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Abstract: *Spectroscopic method in the UV-Vis region is considered the most molecular spectrometric method for content determination of a single component. However, a lot of pharmaceutical dosage forms comprise two or more components which lead to peak overlapping. Moreover, in the chemical stability test, active pharmaceutical ingredient (API) was also found along with the degradation products, impurities, and adulterant compounds. UV-Vis spectroscopy is one of the methods of choice for the determination or quantification of a single component in pharmaceutical preparations. The pharmaceutical products typically contain two or more APIs having chromophoric agents capable of absorbing UV-Vis beams and the absorbance values are summative from the absorption of each UV-Vis active compound according to the additive nature of Lambert-Beer law. The main problem for the simultaneous determination of API along with impurities and the degradation products in pharmaceutical preparations is the presence of overlapping peaks of UV-Vis spectra. The chemometrics-assisted spectroscopy is one of the analytical efforts to solve these problems. This review highlighted the application of chemometrics in combination with UV-Vis spectroscopy for the assay of API, impurities, adulteration issues and degradation products present in pharmaceutical dosage forms.*

Keywords: *UV-Vis spectroscopy; chemometrics; API; degradation products; pharmaceutical dosage forms*

List of Abbreviations

AC	= Acephylline piperazine
ACA	= 4-Chloroacetanilide
ACH	= Acetophenone
AKN	= Alkaline degradation products
ALP	= Allopurinol
AM	= 1-Methyl-3-phenylpropylamine
AME	= Absolute mean error
AML	= Amlodipin
ANN	= Artificial neural networks
AP	= 4-Aminophenol
API	= Active pharmaceutical ingredients
ASP	= Aspirin
ATN	= Atenolol
ATV	= Atorvastatin calcium
B_1	= Thiamine
B_6	= Pyridoxin
BET	= Betamethasone
BX	= Bromhexine hydrochloride
BZ	= Benazepril hydrochloride

BZA = *p*-Hydroxybenzoic acid
CAFF = Caffeine
CAR = Carbidopa
CBM = Carbamazepine
CBME = Carbamazepine epoxide
CBS = Cobicistat
CBT = Carbetocin
CEF = Cefixime
CEL = Celecoxib
CFS = Cefoxitin sodium
CLS = Classical least square
CP = 4-Chlorophenol
CPX = Ciprofloxacin
CRA = Concentration residual augmented
CS = Cromolyn sodium
CTM = Chlorpheniramine maleate
CZX = Chlorzoxazone
DAP = 2,6-Diaminopyridine
DIA = Diacerein
DOX = Doxycycline hyclate
DP = Diprophyline
DPF = Dapagliflozin
DPH = Diphenhydramine hydrochloride
DRV = Darunavir ethanolate
EBV = Elbasvir
EMP = Empagliflozin
ENM = Enalapril maleate
ENT = Entacapone
ERD = Erdosteine
ET = Etodolac
ETB = Emtricitabine
EZT = Ezetimibe
FA = Fenofibric acid
FEN = Fenofibrate
GAANN = Genetic algorithm artificial neural networks
GA-PLS = Genetic algorithm partial least square
GLM = Glimepiride
GLZ = Gliclazide
GMI = Gemifloxacin
GRV = Grazoprevir
GUA = Guaifenesin
HB = *p*-Hydroxybenzaldehyde
HCT = Hydrochlorothiazide
HP = Haloperidol
HPLC = High-performance liquid chromatography
IBU = Ibuprofen
IMB = Imatinib
IMD = Imidapril hydrochloride
ISX = Isoxsuprine
LAM = Lamivudine
LDV = Ledipasvir
LES = Lesinurad
LEV = Levodopa
LS-SVM = Least squares support vector machine
LV = Latent variable
MCR = Mean centering ratio spectra
MET = Metformin hydrochloride
MF = Mometazone furoate
MNZ = 2-Methyl-5-nitro-1*H*-imidazole
MP = Methylparaben
MTZ = Metamizole
NAP = Naproxen
NAPH = Naphazoline hydrochloride
NEO = Neomycin
NF = Norfloxacin
NIF = Nifuroxazide
NLP = Nalbuphine
NMR = Nuclear magnetic spectroscopy
NP = 4-Nitrophenol
ONZ = Ornidazole
OXI = Oxidative degradation products
PC = Principal component
PCR = Principal component regression
PCT = Paracetamol
PH = Phenobarbitone
PHE = Phenylephrine
PHEN = Phenylephrine hydrochloride
PHZ = Phenazopyridine hydrochloride
PIM = Pimozide
PIO = Pioglitazone
PLSR = Partial least square regression
PP = Papaverine hydrochloride
PROPI = Propyphenazone
PrP = Propylparaben
PZ = Prazosin
RAM = Ramipril
RIS = Risperidone
ROS = Rosuvastatin Calcium
RMSEC = Root mean square error of calibration
RMSECV = Root mean square error of cross-validation
RMSEP = Root mean square error of prediction
RSE = Relative standard error
SAX = Saxagliptin
SFB = Sofosbuvir
SL = Salbutamol sulfate
SMLR = Stepwise multiple linear regression
SMT = Simvastatin
SOF = Sofosbuvir
SPR = Spironolactone
SRA = Spectral residual augmented
STA = Stavudine
STG = Sitagliptin
SVR = Support vector regression
TAF = Tenofovir alafenamide fumarate
TC = Thiocolchicoside
THEO = Theophylline

TMP = Trimethoprim
TRM = Tramadol
TZ = Tinidazole
VAL = Valsartan
VDG = Vildagliptin
VEP = Velpatasvir
VNC = Vancomycin
GLZ = Gliclazide

■ INTRODUCTION

Spectroscopy is a discipline concerned with the interaction between electromagnetic radiation in certain wavelengths and samples. Ultraviolet-Visible (UV-Vis) spectrophotometry is a common analytical method used in the routine analytical laboratory and pharmaceutical industry due to its simplicity and rapidity. The versatility of instruments, the simplicity of analytical procedures, and the method performance make UV-Vis spectroscopic method widely used for content determination of pharmaceutical dosage forms. This spectroscopic technique is also more economical compared to other spectroscopic techniques like infrared and NMR and other instrumental methods like chromatography and electrophoresis [1-2]. In UV-Vis spectroscopy, electrons in analytes absorbing UV radiation (200–400 nm) and visible radiation (400–800 nm) are excited from the ground state into excited states. UV-Vis spectroscopy is quantized, in which only electromagnetic radiation with a precise energy level can make electronic transitions [3].

UV-Vis spectroscopy is a method of choice for the determination of a single component in pharmaceutical preparations. Unfortunately, pharmaceutical products typically contain two or more active pharmaceutical products having chromophoric agents capable of absorbing UV-Vis beams [4], causing signal overlapping that challenges the analysis. Quantitative analysis of spectroscopic methods is based on Lambert-Beer's law, which relates to the absorbance and concentration of analytes, as depicted in Eq. (1).

$$A = abc \quad (1)$$

in which A is the absorbance value, a is the specific absorptivity of analytes which depends on wavelength and solvents used, b is the cuvette thickness, and c expresses the concentration of analytes.

The main challenge of UV-Vis spectroscopy for simultaneous quantitative analysis of more than one active chromophoric compound in the same mixtures is the presence of overlapping UV spectra. Consequently, the absorbance value in a certain wavelength is added from each chromophoric compound in the mixture. Under computer-controlled spectrophotometers, some efforts have been made to resolve the overlapping UV-Vis spectra coming from the mixtures of compounds, including derivative spectrophotometry or its combination with chemometrics [5-6], Vierordt's method and its modified method [7], H-point standard addition method [8], and chemometrics of multivariate calibration such as CLS, SMLR, PCR, PLSR, GA-PLS and ANNs [9].

■ METHOD

Reputable databases including Scopus (http://www.scopus.com/), Web of Science (http://webofknowledge.com/), DOAJ (doaj.org), ScienceDirect (http://www.sciencedirect.com/), PubMed (http://www.ncbi.nlm.nih.gov/pubmed), Springer Link (http://link.springer.com/), American Chemical Society (https://pubs.acs.org/), Wiley Online Library (http://onlinelibrary.wiley.com/), recognized books, abstracts and non-indexed journals were explored while searching the literature. The keywords used were "UV-Vis spectroscopy", "Chemometrics", "UV-Vis spectroscopy for assay for Active Pharmaceutical Ingredients", "UV-Vis spectroscopy for assay for Pharmaceutical Products". This procedure was adopted by Hosssain et al. [10].

■ DISCUSSION

Chemometrics

Chemometric methods are powerful tools used in analytical chemistry to extract chemical data into more understandable information. The application of chemometrics in the quality control of pharmaceutical products is continuously increasing due to the advanced development in statistical software and instrumentation that allow the exploration of new issues in analytical

chemistry [10]. The term chemometrics originated from the word *kemometri* (*kemo* refers to chemistry and *metri* refers to measure) and was first introduced by Svante Wold in 1972. Chemometrics is considered an interdisciplinary study combining mathematical and statistical methods with chemistry to extract chemical information from chemical data. Chemometrics is a science related to the measurements of responses, including from UV-Vis spectra, to be extracted into more understandable information [11]. In spectroscopic applications, the chemometric techniques widely used in pharmaceutical analysis are UV-Vis spectral processing, pattern recognition or classification methods, and regression methods using multivariate data [12], as shown in Fig. 1.

Among chemometrics techniques, multivariate calibrations such as CLS, SMLR, PCR, PLSR, GA-PLS, and ANNs [9] are typically used. PCR and PLSR methods are considered inverse calibration methods in which the concentrations in y-axes are modeled using absorbance values in x-axes [13]. The inverse calibration of PLS and PCR in which the concentration (y-axis) is modeled with UV-Vis spectra (x-axis) is the most widely multivariate calibration applied for the quantitative analysis of API, degradation products, and impurities with overlapping UV-Vis spectra. Multivariate calibrations offered reliable prediction models of analytes because they used some absorbances in large wavenumber ranges, thus enhancing the model's accuracy. In PCR and PLSR, the original variables were converted to LVs, and then LVs used as variables to be modeled with analyte concentrations. The phenomena of under-fitting and over-fitting must be considered by comparing the model performances in calibration and validation models [14].

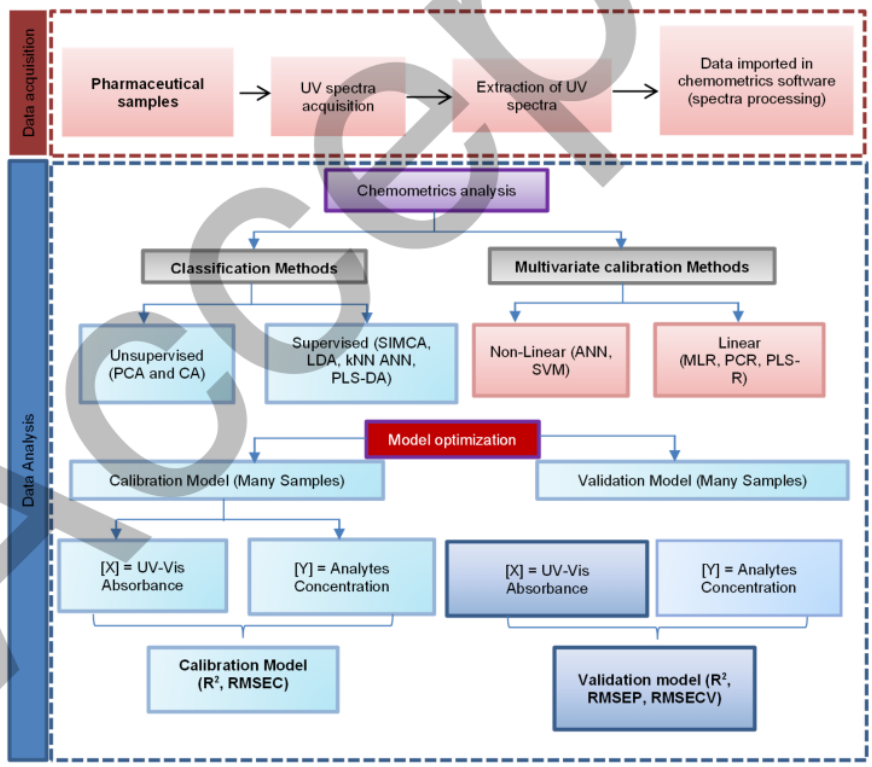

Fig 1. The Schematic representation regarding the chemometrics technique application using UV-Vis spectral absorbances variables. See list of abbreviation

Application of UV-Vis Spectroscopy and Chemometrics for Determination of Active Pharmaceutical Ingredients

The combination of chemometrics with UV-Vis spectroscopy as a non-destructive analytical method has been widely employed to: (1) determine the levels of API in pharmaceutical preparations, (2) quantify APIs and their metabolites in the biological fluids, (3) determine the degradation products of APIs occurring during process and storage, (4) perform the quantitative analysis of impurities in APIs, and (5) identify the counterfeits in pharmaceutical products [15-17].

UV-Vis spectra contain a lot of data that can be used for multivariate analysis. The absorbance values could be extracted for the analytical assay of the targeted compounds. To analyze multiple compounds, chemometrics is required to obtain more selective and sensitive results. The spectra pre-processing treatments could be applied prior to data extraction, such as spectra normalization, baseline correction, and spectra derivatization, to improve the analysis results. Hundreds of variables resulting from data extraction are used for chemometrics analysis. Several data pre-processing could also be applied before chemometrics analysis, such as data scaling and mean-centering to obtain good data variation. For quantitative analysis, multivariate calibrations of PLS and PCR could predict the concentration of compounds with high accuracy and high precision using the optimized variables. PLSR searches the latent variables which have essential roles in concentration prediction. Meanwhile, PCR builds a regression model using factors from principal components generated from variables. The optimization of variables was evaluated using the coefficient of determination (R^2) both in the calibration and validation model to measure good fitness and error values demonstrated by RMSEC, RMSEP, and RMSECV. High R^2 values and low error values are required to be categorized as good models. Chemometrics offers advantages for the simultaneous analysis of analytes. However, the calibration model used for certain pharmaceutical products could not be extended to other formulations with different compositions. Therefore, the different formulas of pharmaceutical products need new model optimization of the multivariate calibrations [18].

Assay of Active Pharmaceutical Ingredients in Pharmaceutical Dosage Form

Table 1 compiled the reported publications regarding the use of UV-Vis spectroscopic methods in combination with multivariate calibrations for the determination of API in raw materials and in pharmaceutical preparations. Multivariate calibration-assisted UV spectroscopy was developed for the simultaneous analysis of four APIs, namely PCT, DPH, CAFF, and PHEN in the tablet. Seventeen samples mixture of these ingredients prepared in different ratios were used for PCR and PLSR analysis. UV measurement was performed at 240–320 nm with an interval of 1 nm. The UV spectra were then extracted for PCR and PLSR analysis. Additionally, HPLC analysis was performed coupled with chemometrics for the assay of PCT, DPH, CAFF, and PHEN. HPLC was carried out in isocratic mode using the mobile phase of MeOH-KH_2PO_4 buffer (pH 3, 10 mM) (50:50 v/v) delivered isocratically at 0.81 mL/min. Compound separation was performed using a Phenomenex ODS column and the detection of analytes was carried out at 220 nm. The HPLC method was validated by determining the performance characteristics, including linearity, selectivity, accuracy, precision, and robustness. The results obtained from UV spectroscopy measurement were compared statistically with the results obtained using the HPLC method. The initial step in UV measurement was wavelength optimization providing the best calibration models providing the best predictive capability between actual and predicted values of analytes using PCR and PLSR, as indicated by the highest R^2 and low RMSEC, RMSEP and RMSECV. Finally, the absorbance values at 240–320 nm applying an interval of 1 nm were selected. The calibration and validation samples were prepared in the concentration ranges of 2–16, 80–400, 4–14, and 20–120 µg/mL for PCT, DPH, CAFF and PHEN, respectively. The results showed that PCR and PLSR showed good accuracy and precision at the selected variables (PCs and LVs) with low values of RMSEC and

Table 1. The use of spectroscopy UV-Vis in combination with chemometrics for determination of active pharmaceutical ingredients in pharmaceutical dosage forms*

Drugs	Chemometrics	Wavelength	Pharmaceutical dosage form	Sample preparation	Results	Ref.
PCT and CAFF	PLSR and ANN	205–300 nm with an interval of 1 nm	Tablet	The calibration and validation samples were prepared in concentration levels of 8.0–40.0 µg/mL (PCT) and 5.0–36.0 µg/mL (CAFF). The powdered tablet was dissolved in methanol.	ANN revealed a better prediction model than PLSR. Using ANN, the R^2-values were 99.28% (PCT) and 99.13% (CAFF). The recovery percentages of PCT and CAFF were 75–86% and 77–92% from labeled claims for PCT and CAFF, respectively.	[34]
PCT, ENM and HCT	MLR, CLS, and TLRC	200–320 nm with an interval of 1 nm	Invozide® tablet containing 325 mg PCT, 25 mg HCT 10 mg ENM	The standard solutions in the range of 5–35 µg/mL (PCT), 1.5–40 µg/mL (HCT) and 5–40 µg/mL (ENM) were prepared. Tablet was powdered, added with methanol 0.1 M in HCl and filtered.	TLRC, MLRC and CLS were accurate and valid for the prediction of these drugs. ANOVA-test revelated that the recoveries obtained using these three methods and HPLC did not differ significantly ($p > 0.05$).	[35]
ET and TC	PLS, PCR, and CLS	Absorbance was measured in 240–440 nm with an interval of 1 nm.	Tablet containing of 400 mg ET and 8 mg TC.	Calibration samples (25 sets) and validation samples (8 sets) in the binary mixture consisting of ET in the range of 15–75 µg/mL and TC in the range of 1–10 µg/mL through factorial design. Methanol is used as extracting solvent. The mixture was sonicated for 15 min.	All multivariate calibrations (PLSR, PCR, and CLS) yielded acceptable validation parameters. PLSR and PCR offered better calibration and validation models. The recovery percentages obtained in tablet using PLS, PCR, and CLS were 98.26, 98.16, and 98.17% for ET as well as 99.14, 98.26, and 98.15% for TC.	[36]
CPX and ONZ.	PLS and PCR	267–330 nm with interval λ of 0.5 nm	Tablet, containing CPX 500 mg and ONZ 500 mg	The calibration and validation sample sets (36 mixtures) with concentration ranges of 2.0–12.0 µg/mL. The powder is dissolved in methanol and sonicated for 15 min.	Both PLS and PCR methods resulted in R^2 of 0.9893–0.9949 either in calibration or validation models. The percentages of recovery were 101.6-102.0%. RMSEP and RMSEC values were 0.26–0.35.	[37]
CPX and DOX	PLSR and PCR	200–400 nm with intervals 2 nm	CPX tablets labeled to contain 500 mg and DOX capsule labeled to contain 100 mg	Calibration and validation samples were prepared in the concentration ranges of 1–10 µg/mL for CPX and 5–25 µg/mL for DOX. The powdered tablets or capsules were added with	PLSR and PCR models previously optimized were accurate and precise for the prediction of CPX and DOX in the samples with recovery percentages of 97.50–101.87% and RSD values < 2%. RMSEP and RMSEC	[38]

				aquadest, ultrasonicated for 15 min, filtrated, and subjected to UV spectra measurement.	values were 0.142–0.208 and 0.278–0.824. High recoveries and low values of RSD, RMSEC and RMSECV indicated that the developed method was acceptable for predicting unknown samples containing CPX and DOX.	
ATV and EZT	PLSR and PCR	230–260 nm with an interval of 0.5 nm	Tablet, containing ATV 10 mg and EZT 10 mg	Twenty-eight (28) calibration sample sets and eight (8) validation sample set at the level of 5.0–30.0 µg/mL were prepared. The powder was dissolved in methanol.	Both PLSR and PCR resulted in recovery percentages of about 100% (for accuracy studies) with RSD values < 2% (for precision studies). The LoD and LoQ values using PLS or PCR were 0.53 and 1.61 µg/mL (ATV) and 0.18 and 0.57 µg/mL (EZT).	[39]
MET and GLZ	PLSR and CLS	220–278 nm with an interval of 3 nm	Tablet Fixed Dose Combination (FDC) containing 500 mg MET and GLZ 30–80 mg	The concentration ranges were 8–20 µg/mL (MET) and 1–5 µg/mL (GLZ). FDC Tablet was powdered, added with MeOH and sonicated for 10 min, filtered, and scanned.	PLSR offered a better accuracy model than CLS. The values of LOD using PLSR were 0.0965 µg/mL (MET) and 0.0441 µg/mL (GLZ).	[40]
PCT, PROPI, and CAFF	PLSR	220–313 nm with an interval of 3 nm	Tablet containing 250 mg PCT, 150 mg PROPI, and 50 mg CAFF	Tablet was powdered, dissolved with methanol, sonicated for 10 min, filtered, and scanned.	The R^2 values for the relationship between actual and calculated values were 0.9994, 0.9878, and 0.9919 for PCT, PROPI, and CAFF, respectively. RMSEC values were 0.027–0.082%. The recovery percentages obtained were 90.70, 90.49, 103.38% for PCT, PROPI, and CAFF from the labeled claim.	[41]
BET and NEO)	PLSR	200–400 nm	Cream containing BET 1 mg and NEO 5 mg	Creams were added with 96% EtOH and homogenized. The mixture was subjected to sonication for 15 min. The standard addition method was used by spiking samples with standard solutions.	The recovery percentages of BET and NEO were 91.35% and 97.56% from labeled claimed. RSD values for BET and NEO were 0.93% and 1.73%. RMSEC values were 0.0230 and 0.3553, with RMSEP values of 0.1558 and 0.0820. The predictive ability of the developed method meets the requirement for cream dosage form according to USP XXX.	[42]
VEP and SOF	CLS, PCR, PLSR and GAPLS	230–400 nm with an interval 1 nm	Tablet consisted of VEP 100 mg and SOF 400 mg.	VEP and SOF were prepared in the levels of 5–9 µg/mL and 24–	The recovery percentages and RSD values of VEP and SOF using CLS, PCR, PLS, and	[43]

				32 µg/mL. The powdered tablet was dissolved in methanol.	GAPLS are acceptable. One-way ANOVA indicated that there is no significant difference ($p > 0.05$) for four recoveries.	
EBV and GRV	ANN and GAANN models	230–400 nm with 1 nm interval	Tablets containing of EBV 50 mg and GRV100 mg.	13 calibration samples and 12 validation samples at levels of 1–9 µg/mL EBV and 6–14 µg/mL GRV. The powdered tablet was dissolved in methanol.	The recovery percentages were in the range of 99.76–100.27%. RMSEC and RMSEP values were 0.1247–0.2968 and 0.2065–0.3018. The results obtained using UV spectroscopy combined with ANN and GAANN do not differ statistically from HPLC method based on ANOVA test.	[44]
LES and ALP	PLSR, PCR, and GAPLS	240–280 nm with an interval of 1 nm	172, Tablets containing 200 mg LES and 300 mg ALP	Thirteen sample mixtures were applied in the calibration set, and twelve samples were used in the validation set at levels of 4–12 µg/mL LES and 6–18 µg/mL ALP. The powdered tablet was dissolved in methanol.	All multivariate calibrations were acceptable, as indicated by R^2 and low values. The mean recoveries for LES and ALP were 99.56 and 99.85 (PCR), 100.63 and 100.73 (PLSR), 100.37 and 100.01 (GAPLS). There is no significant difference ($p > 0.05$) between UV spectroscopy combined with PLSR, PCR, and GAPLS with HPLC method.	[45]
PHEN and CTM	CLS and PCR	200–400 nm with an interval of 3 nm	Sine Up syrup labeled to contain 100 mg% PHEN and 50% CTM	10 calibration solutions and 10 validation solutions with concentrations range 10–60 µg/mL (PHEN) and 4–30 µg/mL (CTM).	Determination of PHEN and CTM in authentic, laboratory-made samples and syrup dosage form using CLS and PCR resulted in acceptable values of recoveries (98.1–100.7%). UV spectroscopy is comparable with HPLC ($P > 0.05$).	[46]
DRV and CBS	CLS and PLSR	UV spectra at 235–285 nm with an interval of 1 nm	Binary mixture and tablets. Tablet consisted of DRV 800 mg and CBS 150 mg.	Twenty-five and eight samples for calibration and validation datasets were designed using the experimental design of a multilevel multifactor with concentration ranges of 5–30 µg/mL either in DRV or CBS.	Both PLSR and CLS methods provide high R^2 (0.996–0.999) for DRV and CBS. PLSR provided better sensitivity and accuracy than CLS. The recoveries of DRV and CBS in tablets using PLS were 99.71 ± 0.13 and 99.27 ± 0.54. ANOVA test informed that there is no significant difference ($p > 0.05$) between UV spectroscopy-multivariate calibrations and HPLC method.	[47]

GLM and PIO	Residual augmented CLS (ARCLS), PCR, and PLSR	215–235 nm in the intervals of Δλ of 0.4 nm	Amaglust® tablets containing 4 mg GLM and 30 mg PIO	Set calibration and validation mixtures were prepared with concentration ranges of 24–60 µg/mL for PIO and 3.2–8 µg/mL for GLM. The powder equivalent to PIO 30 mg and GLM 4 mg was dissolved with ACN, sonicated for 15 min and filtered using filter paper 0.45 µm.	PLSR and PCR were selected because the statistical performances were acceptable, as indicated by high R^2 and low values of RMSEC, RMSEP, and RMSECV. There is no significant difference for mean recovery between the HPLC and UV spectroscopy-PLSR, UV-PCR and UV-ARCLS.	[48]
AML and VAL related	ANN and LS-SVM	200–500 nm with an interval of 1 nm	Tablet dosage forms containing 10 mg AML and 160 mg VAL	The standard solutions used as calibration and validation samples were prepared with levels of 5–25 µg/mL AML and 9–5 µg/mL VAL. Ethanol was used as the solvent.	LS-SVM is the preferred method offering recovery percentages of 100.22% (RSD of 2.719%) for AML and 100.37% (RSD of 0.7342%) for VAL. No significant differences were observed ($p > 0.05$) between HPLC and the proposed method.	[49]
ATN, RAM, HCT, SMT and ASP	PLSR and Genetic algorithms-PLS	210–330 nm with interval of 1 nm	Polycap™ capsules containing ATN50 mg, HCT 12.5 mg, RAM 5 mg, SMT 20 mg and ASP100 mg.	The calibration and validation solutions were prepared in methanol with levels of 6–22, 4–16, 10–30, 10–30 and 2–8 µg/mL for ASP, SMT, ATN, RAM, and HCT, respectively.	The recovery percentages obtained using PLSR, GA-PLS and HPLC methods are not significantly different ($p > 0.05$) using ANOVA test. The recovery percentages of all drugs were in the range of 98.06–100.07%.	[50]
Sulphonamides and TMP	CLS, PCR and PLSR	200–350 nm with an interval of 1 nm	Tablets of Sulphonamides (sulfadiazine, sulfamethoxazole, sulfadimidine and sulphanilamide)	The synthetic mixtures containing these compounds were used in calibration (16 mixtures) and validation (16 samples) models spanning the concentration ranges of 2–6 µg/mL.	PLSR and PCR provide better prediction models than CLS. The percentages of relative errors were 2–10%. The recovery percentages were close to 100% indicating that UV spectra combined with PLS and PCR were accurate and precise for sulphonamides drugs analysis.	[51]
VEP and SOF	ANN and GAANN	UV spectra at 200–380 nm with an interval of 1 nm	Tablets (VEP 100 mg and SOF 400 mg)	Tablet was powdered, added with methanol, filtered, and subjected to UV spectral measurement. The calibration and validation sets were prepared with levels of 5–9 µg/mL VEP and 24-30 µg/mL SOF.	Both methods offered acceptable accuracy and precision with recovery percentages of 99.48–100.75% (VEF and SOF). RSD values were < 2%. No significant difference between the student t-test and the F-test.	[52]
LEV and CAR	PLSR	UV spectra at 200–300 nm and	Five laboratory samples were made	LEV was prepared at 15.4–57.1 µg/mL and	LEV and CAR can be simultaneously analyzed	[53]

		at 300–600 nm after reaction with KIO_4	by mixing LEV and CAR and tablet formulation	CAR at 3.4–17.1 µg/mL. The powder was added with 0.1 M HCl, sonicated for 30 min, centrifugation at 3500 rpm for 15 min and filtered.	using PLSR without sample pre-treatment. No significant difference between the proposed and HPLC methods ($p > 0.05$).	
Quaternary mixture of IMB, GMI, NLP and NAP	PLSR using normal and derivative spectra	200–400 nm with 0.2 nm intervals	Tablets containing 100 mg IMB per tablet, 320 mg GMI per tablet, 500 mg NAP per tablet and ampule containing 20 mg NLP per mL	Concentration of IMB, GMI, NLP and NAP in the calibration and validation sets were 4–8, 3–11, 10–18, and 1–3 µg/mL, respectively. For tablet: the powder was added with MeOH, sonicated for 30 min, filtered, and scanned.	PLSR using original (normal) and first derivative spectra provide a close correlation between predicted values and labeled claims with recovery percentages of 98.5–102.4%.	[54]
EMP and MET	PLS-2	200–300 nm with 0.1 nm intervals	Tablets containing 12.5 mg EMP and 500 mg MET per tablet	Both EMP and MET in calibration and validation sets were prepared in the concentration ranges of 2–10 µg/mL. The powdered tablet was dissolved with methanol.	The levels of EMP and MET in the tablet yielded the mean of the recovery percentages and SD was 95.57% ± 0.49 and 102.16% ± 0.35, respectively using PLS-2 method. T-test of recovery percentages showed no significant difference between UV-PLS-2 and UPLC.	[55]
DP, PH, and PP	PLSR and PCR	200–380 nm with 1 nm intervals	Tablet containing DP150 mg, PH 20 mg, and PP 30 mg.	Calibration and validation sets were prepared using 23 sample mixtures at ranges of 10–25 µg/mL for DP and 1.5–5 µg/mL for PH and PP. Powdered tablet was dissolved with methanol.	Both multivariate calibration methods were reliable for simultaneous quantification of DP, PH and PP as indicated by high R^2 and low values of RMSEC and RMSECV. Student's t-test and the F-ratio showed no significant differences observed ($p > 0.05$) between HPLC and the proposed methods.	[56]
THEO	PLSR	210–350 nm with an interval of 1 nm	Syrup containing 8.0 mg/mL THEO	Syrups containing THEO were subjected to dilution with NaOH 0.1 M.	PLS could accurately predict the levels of THEO in syrup. There is no significant difference for THEO levels using UV spectroscopy-PLS and HPLC methods.	[57]
GUA, SL, with the presence of preservatives of MP and PrP	PLSR and PCR	232–300 nm with intervals of 0.8 nm	Syrup (5 mL) containing GUA 50 mg, SL 2 mg, MP 3 mg and PrP 1.5 mg	A training set of 25 mixtures in calibration and validation sets in 0.1 M NaOH with a concentration range of 20–60, 1–3, 1–5, and 0.6–1.8 µg/mL for GUA, SL, MP, and PrP,	Both methods could provide accurate and precise results with recovery percentages (± SD) of 100.0–100.1% (± 0.15–0.48). One-way ANOVA indicated that both methods were not significantly	[58]

				respectively. Syrup was diluted with NaOH 0.1 M.	different to HPLC method with a P-value of > 0.05.	
AC and BX with the presence of preservatives of MP and PP.	PLSR and PCR	235–275 nm with an interval of 0.4 nm	Each 5 mL Syrup contains AC 100 mg, BX 4 mg, MP 4.5 mg, and PP 0.5 mg.	A training set of 25 mixtures in calibration and validation sets 0.1M HCl in the concentration range of 20–80, 1–5, 1–5, and 0.2–1.8 µg/mL for AC, BX, MP and PP, respectively. Syrup was diluted with HCl 0.1 M.	Both methods could provide reliable results with recovery percentages (± SD) of 99.8–100.1% (± 0.13-2.10). One-way ANOVA indicated that both methods were not significantly different to HPLC method with a P-value of > 0.05.	[58]
LAM and STA	CLS and PCR	200–310 nm with an interval of 1 nm	Tablet containing 150 mg LAM and 30 mg STA	Standard solutions were prepared for calibration and validation sets at levels of 2–12 and 3–15 µg/mL for LAM and STA. The powdered tablet was diluted with 0.1 M HCl, sonicated, and filtered.	The methods were accurate, with acceptable recoveries in most cases. The deviation ranges of LAM and STA between actual and predicted were 0.28% and 1.57% (CLS), 0.03% and 1.77% (PCR), respectively.	[59]
PCT and TRM	PLSR and GA-PLS	200–320 nm with interval 1 nm	Tablets containing PCT 325 mg and Tramadol 37.5 mg.	The working solution was in the range of 15–37 µg/mL for PCT and 1.7–4.3 µg/mL for TMD. A-25 standard mixtures were used in the calibration and validation dataset.	The reliable model was achieved using PLSR method for PCT with a mean recovery of 99.5% and RSE of 0.89%. GA-PLS was the preferred method for TRM with a mean recovery of 99.4% and RSE 1.69%.	[60]
MTZ, B_1, and B_6	Multivariate calibration of PLSR	200–400 nm with a 2 nm interval	The tablet dosage form containing 500 mg of MET, 50 mg of B_1, 100 mg of B_6, and 100 µg of B_{12}	The stock solutions were prepared freshly in HCl 0.1 M and used for preparing 20 calibration samples and 10 validation samples at levels of 9–48, 0.01–0.19, and 2–19 µg/mL for MET, B_{12}, B_1 and B_6.	The methods have good accuracy with R^2 (RMSEP) values were 0.999 (0.3993%); 0.999 (0.1926%); 0.999 (0.1434%) for MET, B_1 and B_6, respectively.	[61]
SFB and LDV	PLS, CWT, and DS	200 to 400 nm with a 1 nm interval	Commercial tablets containing SFB 400 mg and LDV 90 mg.	The calibration and validation datasets were made at ranges of 24–64 and 6–16 µg/mL in ACN for SFB and LDV, respectively.	Each method has a good correlation coefficient with a value of $R^2 > 0.99$. The method was compared with HPLC. ANOVA reveals there are no significant differences among methods ($p > 0.05$).	[62]
RIS and HP	LS-SVM, FIS, ANFIS	200–300 nm	Tablets containing RIS and HP	The standard solutions in calibration and validation datasets were prepared in MeOH at 6–75 µg/mL for RIS and HP.	RMSE values using FIS and ANFIS models were 0.878, 2.124, and 0.285, 0.206 for RIS and HP. ANOVA test exhibited no significant differences between the	[63]

					proposed and HPLC methods.	
VDG, SAX and STG	PLSR, GA-PLS, ANN, and GA-ANN	190–400 nm with 0.5 nm intervals	Januvia® tablets (100 mg STG), Onglyza® tablets (5 mg SAX), Galvus®tablets (50 mg VDG)	Training sets in calibration and validation datasets were prepared at ranges of 10–24–40, and 82–130 µg/mL for VDG, SAX, and STG, respectively.	PLSR, GA-PLS, ANN, and GA-ANN were successfully developed for the prediction of analytes. No different results ($p > 0.05$) between the proposed method and HPLC. RMSEC values were low, indicating a precise method.	[64]
PIM	CLS, PCR, and PLSR	240–370 nm	Orape forte® containing 4 mg of PIM per tablet	The samples was prepared in a concentration range of 30–60 µg/mL PIM in methanol, 20–60 µg/mL in alkaline, and 20–60 µg/mL in Acidic solution.	The proposed method was successful for PIM quantification in tablets without interference. No significant difference ($p > 0.05$) between the proposed and HPLC methods. RMSEP values were 0.0030, 0.0028, and 0.0072 for CLS, PCR, and PLSR.	[65]
PCT, IBU and CAFF	PLSR, GA-PLS, and PC-ANN	200–400 nm with interval of 1 nm	Tablet containing PCT 325 mg, IBU 200 mg and CAFF 40 mg.	Standard solutions were prepared in MeOH -0.1 M HCl (3:1). Two sets of calibration and validation samples were prepared in 25 and 20 mixtures.	UV spectra combined with these multivariate calibrations are accurate and precise methods as indicated by acceptable recoveries and RSD-values.	[66]
AML, VAL and HCT	PLS-1, GA-PLS, ANN, GA-ANN and PCA-ANN	200–400 nm	EXFORGE HCT® tablets containing AML5 mg, Val160 mg, and HCT 12.5 mg.	Training sets used in calibration and validation data sets were prepared in methanol.	The combination of UV spectra and five multivariate calibrations provide an accurate and precise quantitative analysis.	[67]
CEL and DIA	CLS, ILS, PCR, and PLSR	200–400 nm	Capsule OSTEGARD®, Containing 100 mg and 200 mg.	Twenty-five training sets in calibration and validation datasets were prepared in the range of 5–25 µg/mL (CEL) and 3–15 µg/mL (DIA).	The proposed methods provide comparable results, and there are no significant differences among methods ($p > 0.05$).	[68]
HCT and BZ	PLSR and SVR	220–350 nm	Cibadrex® tablets containing 20 mg of BZ and 25 mg of HCT	The stock solutions were made to obtain 100 µg/mL of HCT and BZ and 30 µg/mL of HCT and DSA working solutions. The samples were dissolved in methanol, filtered, and diluted to obtain 100 µg/mL working solution.	UV spectra-multivariate calibrations provide accurate analysis of HCT and BZ in the presence of HCT impurities as indicated by acceptable mean percentage recoveries of 100.01–101.01%, which are comparable to HPLC method.	[69]
SMT and EZT	polynomial least squares based on	200-400 nm	Tablets (40 mg of SMT and 10 mg of EZT), Tablets (20 mg SMT and 10	Stock solutions were made at a concentration of 1 mg/mL of SMT and EZT, respectively.	The proposed method is reliable for the simultaneous determination of drugs in mixtures with acceptable	[70]

	Savitzky-Golay (SG) filters.		mg of EZT), Zocozet tablets (10 mg SMT and EZT)	Working solutions of SMT were made at a concentration of 100 µg/mL of SMT and EZT.	accuracy and precision. The method is successful in the analysis of raw materials and pharmaceutical preparations.	
PAR, GUA, and PHE	CRACLS, MCR-ALS, PCA-ANN	200-400 nm with 2 nm intervals	Panadol® COLD + FLU All in One Tablet (containing 250 mg of PAR, 100 mg GUA, and 5 mg PHE)	The standard solutions were made at 100 mg/mL in MeOH. The calibration and validation samples were made at ranges of 40–50, 16–20, and 1–9 µg/mL for PAR, GUA, and PHE.	The proposed method was valid for the simultaneous determination of PAR, GUA, and PHE in tablets without any separation step.	[71]
ENT, LEV and CAR	Multivariate calibration of PLSR	UV-Vis spectra at 200–600 nm with an interval at 2 nm	Stalevo® tablets (market sample) nominally containing 200 mg ENT, 150 mg LEV and 37.5 mg of CAR per tablet	The standard solutions of ENT, LEV and CAR at 100, 300, and 300 µg/mL were dissolved in methanol-water (7:3).	The developed method was reliable for simultaneous quantitative analysis of drugs in tablets without any separation step.	[72]
DPF and SAX	FZM, FDM, and FRM	200-400 nm	Onglyza® tablets contain 5 mg SAX and Forxiga® tablets contain 10 mg DPF per tablet.	The stock solutions were made at a concentration of 1 mg/ML of each DPF and SAX, and each working solution were made at a concentration 0.1 mg/mL.	The methods provide good accuracy and precision for the simultaneous determination of drugs over the concentration ranges of 2.5–50.0 (DPX) and 2.5–60.0 µg/mL (SAX).	[73]
CEF and ERD	CLS and PLSR	200-400 nm	Suprax® 200 capsules labeled to contain 223.8 mg CEF/capsule and Mucotec® contain 300 mg ERD/capsule	The standard solutions of CEF and ERD were prepared in 1 mg/mL concentration. The working solutions were made at concentration ranges of 20–30 (CEF) and 15–45 µg/mL (ERD).	The developed method was reliable for the simultaneous determination of drugs in dosage form with acceptable recoveries. The accuracy and precision of the proposed method were comparable with the HPLC reference method.	[74]
AML, CEL, and RAM	ACM	210–400 nm	Cardace®AM tablets containing AML 10 mg and RAM 10 mg.	The standard stock solutions were made in 100 µg/mL concentration for AML and CEL. The sample solutions were prepared at 5–60, 5–30 and 5–110 µg/mL for AML, CEL and RAM.	The LoD is 0.5781–0.7132, 0.6497–1.0450, and 0.0001–0.0003 µg/mL for AML, CEL, and RAM. No significant difference between the proposed method and the reference method ($p > 0.05$).	[75]
VNC and CPX	PLSR and ANN	190-400 nm	Vancomycin with 99.80% purity and Ciprofloxacin with 99.30%	The stock solutions were made in 100 µg/mL concentration. The working solutions were prepared in the concentration range 3–30 and 1–10 µg/mL for VNC and CPX.	The methods have high %recovery, 98.79 and [illegible]23% for VNC and CPX. There are no significant differences between the proposed and reference methods. The RMSEP values for PLS-1 were 0.07 and 0.06% for VNC and CPX and	[76]

					the RMSEP values of ANN were 0.12 and 0.11% for VNC and CPX.	
AML and MET	Isosbestic point and dual-wavelength methods	200–400 nm	Amlodipine besylate (99.40%) and metoprolol succinate (99.20%)	The standard solutions were made in 100 µg/mL concentration. The sample solutions were made at 2–25 and 2–30 µg/mL for AML and MET.	The developed method (UV spectra-chemometrics) was reliable for the simultaneous determination of AML and MET.	[77]

*See list of abbreviation

RMSECV. The R^2 values obtained were 0.9991–0.9999 either in calibration or validation models using PLSR and PCR. An assay of pharmaceutical drugs revealed that the recoveries of drugs were 101.076–103.603% (PCR) and 100.943–103.814% (PLSR), respectively. On the other hand, validation analysis using HPLC also revealed good linearity (> 0.999), good precision showed by the RSD value of less than 2%, as well as good accuracy demonstrated by the recovery values (100.85 ± 0.59 for PCT; 101.72 ± 0.31 for DPH; 101.93 ± 0.43 for CAFF; 102.91 ± 0.65 for PHEN). Statistical analysis using One-way ANOVA (p = 0.05) revealed that recoveries obtained using UV spectroscopy-PLSR, UV spectroscopy-PCR, and HPLC methods were not significantly different (p > 0.05). It can be concluded that the combination of UV spectroscopy and chemometrics (PLSR and PCR) can be used as an alternative method to HPLC with the main advantages of simple, rapid, inexpensive and not requiring a sophisticated instrument [14].

Analysis of APIs in Biological Fluids

The combination of UV-Vis spectroscopy with chemometrics of PLSR has been used for quantitative analysis not only in pharmaceuticals but also in biological fluids. Analysis of CBM in the presence of the main metabolite of CBME in human serum was successfully performed using absorbance values of second derivative spectra at the wavelength range of 280–350 nm with interval 1 nm. The use of the second derivative could eliminate the shift baseline effect present in the original UV spectra. The extraction of CBM and CBM-EP was done using benzene. Recovery percentages obtained in spiked plasma samples with 4 different levels of CBM using the proposed method were in the range of 98.0–101.7% with low relative percentage difference, indicating acceptable accuracy and precision. Statistical evaluations using Student's t-test and F-test revealed that both methods did not reveal a significant difference at a confidence interval of 95% (p > 0.05). From this result, UV spectroscopy combined with PLS could be an alternative method for the determination of API in biological fluids with the presence of API's metabolite [63]. PLS using the variable of absorbance values at 190–350 nm with an interval 1 nm was also successful for the determination of CBM along with its metabolite (CBME). The mean recovery percentages for the determination of CBM and CBME were also performed using reference HPLC methods as a comparison to the proposed method (PLSR-UV spectra). The results showed that the recovery percentages of CBM and CBME in synthetic mixtures were 102.57 and 103.00% (for PLS) and 99.40% and 102.20% (HPLC), respectively. Based on the statistical test, there are no significant differences between CBM and CBME using PLSR-UV and HPLC methods (p > 0.05) [19]. UV-spectroscopy and PLSR were also successful in the analysis of amoxicillin and its metabolites in human urines with acceptable validation performance [20].

Analysis of API and Its Degradation Products

UV spectroscopy using MCR and multivariate calibrations of PLSR and PCR was successfully applied for simultaneous analysis of CS and its alkaline degradation products identified as Deg-1 and Deg-2 as shown in Fig. 2. UV spectra revealed the extensive overlapping, therefore the chemometrics was applied to

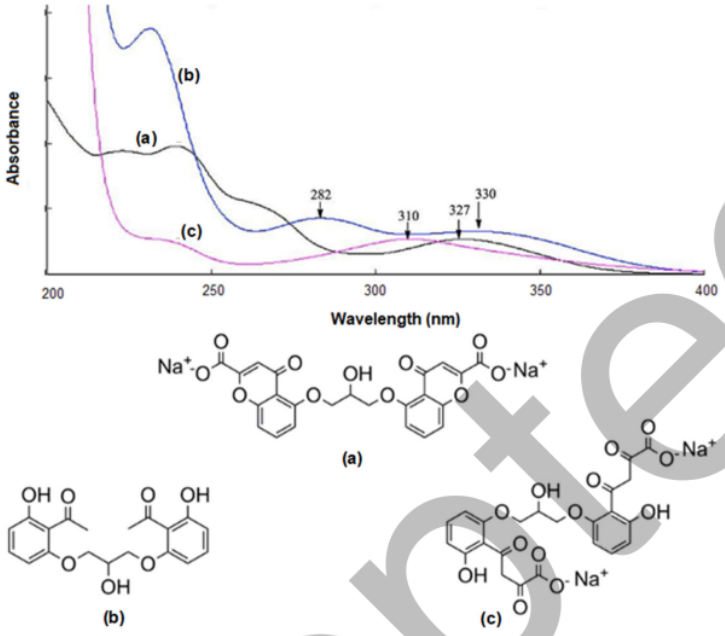

Fig 2. UV spectra and chemical structures of Cromolyn Sodium (a) and its degradation products identified as Deg-1 (b) and Deg-2 (c) scanned at 200–400 nm. Taken with CC-BY license

facilitate the quantification of analytes. The absorbance values after MCR at 367.8, 373.8, and 310.6 nm were used within linear concentration ranges of 2–40, 5–40, and 10–100 µg/mL for CS, Deg-1, and Deg-2, respectively. Using MCR method, the recovery percentages ± SD obtained were 99.91 ± 1.33, 100.28 ± 1.44, and 100.61% ± 1.55 for CS, Deg-1, and Deg-2, respectively indicating that MCR is an accurate and precise method for stability-indicating assay of CS, Deg-1 and Deg-2. PCR and PLS-2 models using variables of absorbance values at wavelength 230–400 nm with 0.2 nm intervals (851 data points) at concentration ranges of 5–13 (CS), 8–16 (Deg-1), and 10–30 µg/mL (Deg-2). The developed method has been successfully used for quantitative analysis of CS and its degradation products in eye drops dosage form. The levels of CS in eye drops dosage form (labeled to contain 40 mg of CS/mL) were 102.40 ± 0.83 and 101.75% ± 0.69 from the claimed label [21].

The UV-Vis spectroscopy and chemometrics method were performed for the determination of MF in the presence of its degradation product. The study was conducted in a forced degradation study of MF performed in basic conditions. Samples were scanned at the range of 220–350 nm. The UV spectra of mixtures of MF with its degradants were used for the quantification of MF. Chemometrics of PLS regression was carried out for the determination of MF concentration. The calibration model demonstrated a good mean recovery of 100.2% with low error indicated by the low value of RMSEC (0.002%). Meanwhile, the mean recovery of the validation model was 97.24%, with RMSEP of 0.04%. The recoveries obtained from sample measurement ranged from 98.47–102.66% indicating no interference from the MF degradation products [22].

UV-Vis spectrophotometry and chemometrics have also been used for the analysis of paracetamol in the presence of its degradants resulting from the basic condition. PCA was performed to differentiate compounds obtained from UV-Vis measurement. The results of PCA suggested the presence of four compounds, namely a reactant (PCT), a degradant, and two intermediate compounds. Chemometrics of MCR-

ALS was further used to confirm the results from PCA. MCR-ALS was aimed at the constraint of non-negativity, either spectral or concentration profiles. Besides, it was also used for the unimodality of the concentration profiles. Results demonstrated that chemometrics of MCR-ALS had a similar result to PCA, recognizing the presence of four compounds. The study was compared using HPLC measurement and it proved the presence of two intermediates. The concentration profiles obtained from UV-Vis and MCR-ALS were in agreement with those obtained from HPLC measurement [23].

UV-Vis spectrophotometry method combined with MCR-ALS has been used to analyze tamoxifen and its degradation products. The acquisition of the UV-Vis spectra was conducted from 0 to 160 min using an irradiation power 400 W/m^2 and from 0 to 120 min at irradiation power of 765 W/m^2. The degradation process could be observed by UV-Vis spectra indicated by the changing of spectra profiles. The use of chemometrics MCR-ALS using variables of absorbance extracted from UV-Vis spectra demonstrated four species of degradation products of tamoxifen as the impurities. It suggested that UV-Vis spectrophotometry method combined with chemometrics of MCR-ALS could be used for the analysis of tamoxifen and its degradation products [24]. Table 2 demonstrates the summary of some analysis of API and its degradation products in pharmaceutical dosage form using a combination of spectroscopy UV-Vis and chemometrics.

Analysis of API and Its Impurity

Combination of UV spectroscopy and multivariate calibration is applied for simultaneous analysis of NF, TZ and impurity of TZ, namely MNZ. Three multivariate calibrations, namely CLS, PLSR and SVR were used for making calibration and validation models for three compounds. The 16 calibration samples and 18 validation 8 samples sets were prepared in the concentration ranges of 4.0–6.5 (NF), 6.0–10.0 (TZ), and 0.10–0.17 (MNZ) µg/mL. The variables used were absorbance values at 220–360 nm using a 1 nm interval. PLSR and SVR revealed better prediction models; therefore, both multivariate calibrations were used for the prediction of NF, TZ and MNZ in tablets. The analytical results using PLSR and SVR on commercial tablets (Tinidol Plus®) exhibited acceptable recoveries (97.84–101.33%) with RSD values less than 2%. Statistical tests of mean recoveries using the independent-t test for both multivariate calibrations did not differ significantly ($p > 0.05$), while ANOVA test for mean recoveries of UV spectroscopy-PLSR, UV spectroscopy SVR and HPLC method was not different significantly with P-value of 5.050 ($p > 0.05$). This indicated that the combination of UV spectroscopy and PLSR/SVR could be an alternative method over HPLC for simultaneous analysis of API and its impurity [25].

The chemometrics models of PLSR and ANN models were optimized and developed for the simultaneous determination of PCT and CZX along with their related impurities namely AP, ACA, NP, CP and ACP. PLS and ANN were compared using all UV spectra at the wavelength range of 200–400 nm and using wavelength of 220–360 nm based on wavelength selection using GA. Therefore, four models were compared namely PLSR, GA-PLS, ANN and GA-ANN. All analyzed compounds and capsules containing PAR and CZX were dissolved in methanol. Fifteen calibration models and 9 validation models were constructed consisting of 8–16 (PAR), 6–22 (CZX), 2–6 (AP, CA, NP and CP), and 5–13 (ACP) µg/mL. The four chemometrics models were successfully used for quantitative analysis of PAR and CZX either in raw materials or in the pharmaceutical dosage form. The recovery percentages for the accuracy study were in the range of 98.62–102.7% for PAR, CZX, AP, CA, NP, ACP, and CP, with RSD values of < 3.00%. The statistical test using one-way ANOVA revealed that the mean recoveries of the developed methods and HPLC method for PAR and CZX are not significantly different ($p > 0.05$). It can be concluded that the proposed method can be easily applied for the simultaneous determination of PAR and CZX without any separation [26].

UV-Vis spectrophotometry method combined with chemometrics has been used for determining NIF and impurities. Spectra acquisition was carried out using a double-beam UV-Vis spectrophotometer with a spectral band of 2 nm employing a scanning speed of

Table 2. The use of spectroscopy UV-Vis in combination with chemometrics for the determination of active pharmaceutical ingredients and its degradation products in pharmaceutical preparations*

Drugs and degradation products	Chemo-metrics	Wave-length	Pharmaceutical dosage form	Sample preparation	Results	Ref.
CFS and Deg-CFS	PCR, PLS, GA-PLSR, ANNs, GA-ANNs, and CLS	200 to 400 nm, with an interval of 1 nm	IV injection and IV infusion containing 1 g CEF per vial.	Alkali degradation product of CFS was prepared by refluxing CFS with 0.1 M NaOH for 10 min. The calibration and validation solutions were in the range of 16–24 µg/mL CFS and CFS-Deg.	All chemometrics techniques provide acceptable accuracy and precision. The percentage recoveries for CFS using PCR, PLS, GA-PLS, ANNs, GA-ANNs, and CLS were 100.98, 100.31, 100.54, 99.53, 100.36, and 100.98%, respectively.	[78]
ISX and its photodegradation products, namely ACH, AM, BZA and HB	PLSR, GA-PLS, ANN and GA-ANN	200 to 400 nm with interval of 0.1 nm	Tablets comprising 20 mg ISX	The standard solutions for calibration and validation sets were prepared in the ranges of concertation ranges of 10–20 (ISX), 1–3 (ACH and HB), 100–140 (AM) and 1–5 (BZA) µg/mL. The powdered tablet was added with methanol, sonicated for 10 min, centrifuged at 4000 rpm, and clear supernatant was subjected to UV spectral measurement.	The chemometric methods have been successfully applied for the evaluation of stability, indicating methods for the simultaneous quantitative determination of ISX and its photothermal degradation products either in bulk materials and/or in tablets. One-way ANOVA test indicated that the proposed methods did not differ significantly ($p > 0.05$)	[79]
NAPH, CTM, and NAPH-Deg	PLSR and PCR	200 to 400 nm with an interval of 2 nm	Eye/nose drops labeled to contain 0.5 mg/mL NAPH and 0.5 mg/mL CTM	25 synthetic mixtures for calibration and validation sets were prepared in 5–25, 5–25 and 5–13 µg/mL for NAPH, CLO, and NAPH-Deg. Eye drop samples were diluted with methanol	Three methods (HPTLC, PLS and PCR using normal and derivative spectra) were successfully applied for simultaneous analysis of NAPH, CTM, and NAPH-Deg with acceptable accuracy and precision. Based on the t-test and F-test, mean recoveries and SD of three methods revealed no significant difference ($p > 0.05$)	[80]
IMD in the presence of AKN and OXI	PLSR and PCR	205–305 nm with an interval of 1 nm	Tablets containing 10 mg IMD	25 synthetic mixtures for calibration and validation sets were prepared in 12–18 µg/mL for IMD, 2.4–3.6 µg/mL for AKN and OKI	Both multivariate calibrations offered acceptable accuracy and precision as indicated by recovery percentages of 99.96–100.09% and RMSEP value of 0.004–0.012. There is no significant difference between PLS-UV, PCR-UV and HPLC methods ($p > 0.05$).	[81]
ROS and FEN along with ROS-Deg and FA	PLS and PCR	200–400 nm with	Tablets containing 5 mg	The concentration ranges of mixtures used in calibration and validation	PLSR and PCR-assisted UV spectroscopy was successfully applied for the determination	[82]

		wavelength interval 1 nm	ROS and 160 mg FEN	sets were 2.00–18.00 (ROS), 5.00–17.00 (FEN), 2.00–4.00 (FA) and 2.00–10.00 µg/mL (ROS-Deg). The powdered tablet was dissolved in methanol	of drugs with recovery percentages of 99.30–100.45% with SD values of 0.547–1.591. No significant differences among PLSR-UV, PCR-UV, and HPLC methods ($P > 0.05$)	
ETB and TAF	ANN, PLSR, and PCR	200–400 nm with a wavelength interval of 2 nm	Tablet containing ETB 200 mg and TAF 25 mg per tablet	30 synthetic mixtures were produced randomly in different concentrations. 19 and 11 synthetic mixtures for calibration and validation set were prepared in the concentration range of 5–18 (EMT) and 5–40 µg/mL (TAF). Stock solutions dissolved with distilled water.	Based on LM and GDX algorithms layer = 5 with neuron 3 and layer = 7 with neuron 7 were considered as the best layers of FM for ETM and TAF, respectively. The best number of components of ETB is 7 and 11 for PLS and PCR methods, with RMSE 0.0160 and 0.0158, respectively. The best number of components for TAF is 5 and 6 in PLS and PCR techniques with RMSE 0.2432 and 0.2815.	[83]
PCT, GUA and CTM	PLS	200–400 nm with a wavelength interval of 2 nm	Twenty different tablets containing PCT, GUA, and CTM	30 mixtures for calibration and validation were prepared to contain 2–15 (PCT), 3–19 (GUA), and 2–20 (CTM) µg/mL in methanol: hydrochloric acid 0.1 M (3:1). The solution is shaken vigorously for 30 min and filtered for UV measurements.	UV spectrophotometry combined with PLS can be used for quantitative analysis of PCT, GUA, and CTM with R^2 for the relationship between actual values and predicted values was 0.999972, 0.999826, 0.999725 and the RMSEC values of 0.022019, 0.067889, 0.083875, respectively.	[84]
HCT and SPR	PLSR and GA-PLSR	216–300 nm with wavelength interval 0.4 nm	Tablet containing 25 mg of HCT and SPR	30 concentration mixtures for calibration and validation were prepared to contain 2.00–6.00 (HCT), 3.00–7.00 (SPR), and 1.00–5.00 (CT, DSA, and SPR deg) µg/mL.	The developed method provides reliable results for the simultaneous determination of HCT, SPR, and its degradation products and its impurities with R^2 of 0.9994 and 0.9987 for HCT and SPR.	[85]
HCT and SPR	CLS, ILS, PCR and PLS	220–290 with wavelength interval 2 nm	Tablets containing 25 mg SPR and 25 mg HTC per tablet	25 standard synthetic mixture for calibration and validation sets containing SPR and HCT was prepared at level of 2-20 µg/mL.	Four chemometrics methods applied to UV spectra were successful for the simultaneous determination of drugs in mixtures and tablets with R^2 for calibration and validation of > 0.99 and the lowest error. ANOVA test exhibited no significant difference among the methods ($p > 0.05$).	[86]
CBT and MET	PCA and PLSR	190–600 nm with wavelength	Injection solution containing	The central composite design was used for optimization of the	The combination of UV-Vis spectra and chemometrics was reliable for determining the	[87]

	interval 0.5 nm	0.100 mg CBT and 1 mg MET	developed method. 90 and 12 samples for calibration and validation were prepared. The tablets were dissolved in a buffer solution.	content of CBT and MET in injection solution with R^2 and RMSE of 0.991 (1.2), 0.989 (1.34) for calibration, and 0.993 (1.21), 0.989 (1.11) for validation, respectively.

*See list of abbreviation

2800 nm/min. Chemometrics of CRACLS and SRACLS were used for the analysis of NIF and its four carcinogenic impurities. The impurities are named as (*S*[4-hydroxy benzohydrazide(*p*-hydroxybenzohydrazide)], [methyl 4-hydroxybenzoate], [(5-nitrofuran-2-yl)methylidene diacetate], and [(*E*,*E*)-*N*,*N*-bis[(5-nitrofuran-2-yl)methylidene]hydrazine(5-nitrofurfuralazine)] and they are coded as A, B, C, and D,respectively. Chemometrics of PLSR was also performed for comparative study purposes. The concentration range of NIF from 10.00 to 50.00 µg/mL was used for creating regression models. Meanwhile, the concentration range of impurities A and B was 0.05 to 0.45 µg/mL and for impurities, C and D was 0.10 to 0.90 µg/mL. Result revealed that chemometrics of CRACLS, SRACLS, and PLSR was successfully used to determine NIF and its four impurities either in the pharmaceutical formulation or in the prepared mixtures [27].

Simultaneous determination of PHZ and TMP in the presence of phenazopyridine HCl impurity, namely DAP has been performed using spectroscopy UV-Vis combined with univariate and multivariate analysis. The univariate method was performed for the determination of phenazopyridine at the wavelength of 412 nm in the concentration range of 1.00–10.00 µg/mL. Univariate method was also successfully used for determination of PHZ, TMP, and DAP. For multivariate analysis, chemometrics multivariate calibration of PLS and PCR was applied for the determination of PHZ and TMP in the presence of DAP. Result demonstrated that PLS and PCR could be used for simultaneous determination of PHZ and TMP in the presence of DAP at the concentration range of 24.00–56.00 µg/mL of TMP. The proposed method was successfully applied to determine the concentration of PHZ and TMP in the pharmaceutical formulation [28].

Detection of Counterfeit Pharmaceutical Products

The presence of Counterfeit pharmaceutical products is a global problem, not only in developing countries but also in developed countries. The United States Food and Drug Administration (FDA) estimates that counterfeits make up more than 10% of the global medicines market [29]. The counterfeits include drugs without sufficient active ingredients, without any active ingredients, or fake packaging [30].

The use of UV-Vis spectroscopy method has been applied for the analysis of counterfeit in acetaminophen. Samples were prepared by mixing binary mixtures of pure acetaminophen with other compounds as adulterants, namely cement, rice flour, vitamin C, and lactose in several concentration levels. The mixtures were dissolved in three different solvents; H_2O (neutral), 0.1 M HCl (acid), and 0.1 M NaOH (alkaline). The samples were scanned using UV-Vis spectrophotometer at a wavelength of 240–500 nm. The concentration used was ranging from 0.01–0.04 mg/mL). Results revealed that the presence of adulterants decreased the absorption of acetaminophen at 254 nm while other parts showed a slight increase in the spectrum. This method here could be used for the quality control of API from counterfeit adulterants [31].

UV-Vis spectroscopy method has been used for the analysis of PCT tablets to determine the concentration of PCT compared to its label. The tablet samples were obtained from several countries on several continents, including Africa, Asia, Europe and Caribbean Island. Sample preparation was performed to extract PCT from tablets. Samples were then analyzed using UV-Vis spectrophotometer method at a wavenumber of 244 nm. It was found that in some samples from different countries, PCT tablets contained an insufficient level of PCT. The actual concentration obtained from the

measurement did not match the label claim. It suggested that UV-Vis spectrophotometry method is the potential to be used for analysis of counterfeit drugs in quality control of API concentration. Another drug successfully studied using UV-Vis spectrometry has been carried out on Tylenol. UV-Vis spectrophotometry could separate peaks of Tylenol and its ingredients, and the concentration of Tylenol could be determined accurately [32].

Determination of TZ in the presence of PZ as a counterfeit drug has been performed using UV-Vis spectrophotometry and chemometrics of machine learning. Spectra acquisition was carried out in absorbance mode at intervals of 0.1 nm. The region used for measurement was 200–400 nm. Machine learning was performed for the determination of PZ and TZ at five concentration levels. The variables used for creating a machine learning model were absorbance values selected using a variable selection algorithm to obtain the most important variables. Machine learning method was evaluated using RMSE, R^2, and AME. Result showed that the linear model provided the best prediction model among other models. The obtained RMSE, R^2, and AME for the training dataset or calibration model were 0.159, 0.997, and 0.131, respectively, whereas for the prediction model or test dataset, the RMSE, R^2, and AME were 0.196, 0.99, and 0.161, respectively. The model could be applied for the determination of PZ in the presence of TZ in all the pharmaceutical formulation samples [33].

■ CONCLUSION

The development of analytical methods for quality control of pharmaceutical products has grown rapidly. UV-Vis spectrophotometry method has become a method of choice for the analysis of API in pharmaceutical products. It offers rapid analysis as well as easy sample preparation and it can be applied for wide range of API analysis. Moreover, it has been used for routine analysis for quality control purposes of pharmaceutical products. Combined with chemometrics of multivariate analysis including pattern recognition such as PCA, LDA, and PLS-DA as well as multivariate calibration such as PLS, PCR, and MCR-ALS, UV-Vis spectrophotometry method could be an ideal technique for quality control of pharmaceutical products. Some spectra pre-treatment techniques in chemometrics, such as baseline correction, normalization, and derivatization, could be used to improve the simultaneous analysis of compounds. The data treatment on chemometrics such as scaling, is widely used to obtain a good variety of multivariate data. Chemometrics model evaluation could be performed using R^2 of calibration and validation to evaluate model fitting. Meanwhile, RMSEC, RMSECV, and RMSEP were used for the evaluation of model error and precision. This technique can be applied to analysis of API in pharmaceutical products and analysis of API in biological fluids. Moreover, it can be used for analysis of API in the presence of degradation products, impurities, and detection of counterfeit pharmaceutical products. Therefore, it suggested that a combination of UV-Vis spectrophotometry and chemometrics method has been proved as a good analytical technique for quality control of pharmaceutical products.

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