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Design, optimization, and validation of chemometrics assisted spectrophotometric methods for simultaneous determination of brexpiprazole and aripiprazole

Parth Patel and Rajashree Mashru

Abstract
Four chemometrics methods were applied to simultaneous determination of Brexpiprazole and Aripiprazole in simulated mixture. Classical least-square (CLS), inverse least-square (ILS), principal component regression (PCR) and partial least-square (PLS) methods do not need any priori graphical treatment of the overlapping spectra of two drugs in a mixture. For all chemometrics calibration a concentration set of the random mixture consisting of the two drugs in methanol was prepared. The absorbance data in the UV spectra were measured for the 23 wavelength points (from 240 to 350 nm) in the spectral region 200-400 nm considering the intervals of $\Delta\lambda$=5nm. The calibration of the investigated methods involves only absorbance and concentration data matrices. The developed calibration were tested for the simulated mixtures consisting of two drugs and using MATLAB 2012b and unscrambler x software the chemometrics calculations were performed. In conclusion, it is claimed that these new chemometrics-assisted spectrophotometric methods are inexpensive, rapid, and simple and can be trustfully carried out in quality control laboratories.

Keywords: Chemometrics calibration methods, brexpiprazole, experimental design, aripiprazole

Introduction
Chemometrics methods are one type of multivariate analysis i.e. considering more than one variable at a time. When applied to UV spectrophotometry, many wavelengths are taken as variable and absorbance at each wavelength is considered. Least square approach involves mathematical modelling by which the square of residual (difference between actual and predicted concentration) is minimized to lowest level. Four different chemometrics methods are used which are

1. Classical Least Square
2. Inverse Least Square
3. Principal component Regression
4. Partial Least Squares or Projection to Latent Structures

These methods first calibrate the mathematical model by using absorbance data of calibration standards with known concentration and then predict the concentration of unknown samples from their absorbance data. If there are m number of calibration standards and l chemical components (drugs) and n is the number of wavelengths considered, all methods involve presentation of absorbance data as a matrix with m rows and n columns, concentration data as a matrix with m row and l columns [1]. Brexpiprazole, an atypical antipsychotic, is available as REXULTI® (Brexpiprazole) tablets. Chemically Brexpiprazole was 7-{4-[4-(1-Benzothiophen-4-yl) piperazin-1-yl] butoxy} quinolin-2(1*H*)-one. The empirical formula is C25H27N3O2S and its molecular weight is 433.57g/mol. It is used in the treatment of schizophrenia and as an adjunctive therapy to antidepressants for the treatment of Major Depressive Disorder (MDD). The mechanism of action of brexpiprazole in the treatment of major depressive disorder or schizophrenia is unknown. However, the efficacy of brexpiprazole may be mediated through a combination of partial agonist activity at serotonin 5-HT1A and dopamine D2 receptors, and antagonist activity at serotonin 5-HT2A receptors [2]. Aripiprazole is an atypical antipsychotic drug that is available as ABILIFY® (Aripiprazole) Tablets, ABILIFY DISCMELT® (aripiprazole) Orally Disintegrating Tablets, ABILIFY® (aripiprazole) Oral Solution, and ABILIFY® (aripiprazole) Injection, a solution for intramuscular injection. Aripiprazole is 7-[4-[4-(2, 3-dichlorophenyl)-1-piperazinyl] butoxy]-

3, 4 dihydrocarbostyril. The empirical formula is C23H27Cl2N3O2 and its molecular weight is 448.38 g/mol. It is used in the treatment of schizophrenia, acute treatment of manic and mixed episodes associated with Bipolar disorder. The mechanism of action of aripiprazole in schizophrenia or bipolar mania, is unclear. However, the efficacy of aripiprazole in the listed indications could be mediated through a combination of partial agonist activity at D2 and 5-HT1A receptors and antagonist activity at 5-HT2A receptors [3].

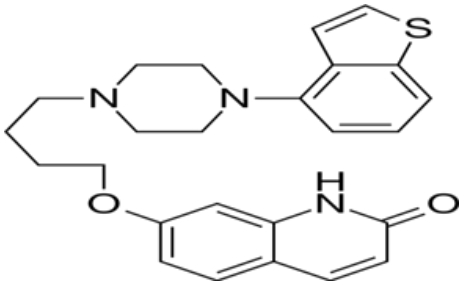


Fig 1: Chemical structure of Brexpiprazole

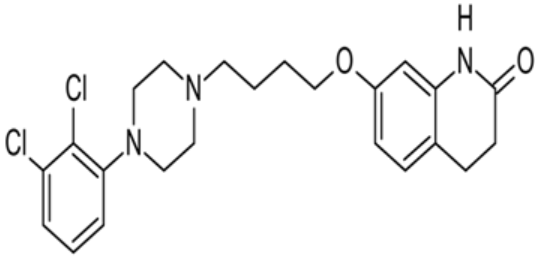


Fig 2: Chemical structure of Aripiprazole

Why this combination? [4]

1. Schizophrenia has a prevalence rate of 1% and is a complicated illness that often leads to periods of relapses. Up to a third of patients with schizophrenia are considered to be treatment-resistant. Despite the new and various antipsychotic medications that have recently come to market, the number of treatment-resistant cases continues to abound. This has led to a sub-population of patients with schizophrenia being treated with more than one antipsychotic medication concurrently. Though it has become more common in clinical practice, there is sparse literature to objectively support the combination use of antipsychotic medications.
2. There is also little literature addressing the use of a Long-Acting Injectable (LAI) used in combination with another atypical antipsychotic. This case report serves to highlight the concurrent use of aripiprazole LAI used in combination with oral brexpiprazole in two patients with treatment-resistant schizophrenia. The receptor binding affinity of these two antipsychotics appears complementary and perhaps even protective for extra pyramidal symptoms (EPS).
3. We hypothesize that the use of a LAI serves as a "foundational barrier" to mitigate the potential for full psychotic relapses that patients become noncompliant with their oral medications, and that the LAI also may help with oral medication compliance in this subpopulation of treatment-resistant schizophrenia patients by increasing baseline functionality.
4. Preclinical trial for this combination implies that it may provide significant therapeutic effects with favourable safety profile

Several UV methods reported for Brexpiprazole. HPLC method reported for estimation of Brexpiprazole in bulk and tablet dosage form [5-7].
Several UV methods also reported for Aripiprazole. HPLC method reported for estimation of Aripiprazole in bulk and also injectable formulations [8-10]. There is no single method is reported for simultaneous estimation of Brexpiprazole and Aripiprazole in simulated mixture

Materials and Methods

Instrumentation and software

UV spectral studies were done using Shimadzu UV-1700 double beam spectrophotometer connected to a computer loaded with Shimadzu UV probe 2.10 software. The absorbance spectra of drug were carried out in 1 cm quartz cells over the range of 200-400nm. The samples were weighed on electronic analytical balance (A×120, Shimadzu). MATLAB 2012b used for CLS and ILS & UNSCRAMBLER X used for PCR and PLS. Data extraction from UV probe 2.10 software to UNSCRAMBLER X was done using Microsoft Excel for Mac Version 16.34.Design of Calibration and Validation set was done using DESIGN-EXPERT 11.

Reagents and Chemicals

Methanol analytical reagent grade (Research Lab fine chem industries, Mumbai, India) was used as the solvent and diluent.

Preparation of Standard stock solution

10 mg of Brexpiprazole and Aripiprazole were weighed accurately and transferred into 10 ml volumetric flask separately. Methanol was added into the volumetric flask to dissolve the standards and finally volume was made up to the mark with Methanol to obtain standard solutions of Brexpiprazole and Aripiprazole (1000mcg/ml).

Preparation of working standard solution

From the stock above solution of Brexpiprazole and Aripiprazole, Working standard solution of Brexpiprazole and Aripiprazole (100 mcg/ml) was prepared by transferring 1 ml aliquot to 10 ml volumetric flask separately and making up the volume with methanol.

One-component calibration

This was examined in the concentration range of 1-5 mcg/ml for Brexpiprazole and 5-25mcg/ml for Aripiprazole. Absorbance values were recorded at λmax of each drug (325 nm for Brexpiprazole and 255nm for Aripiprazole) against methanol as blank. Linear dynamic range for each drug was studied by least square linear regression of concentration and the corresponding absorbance.

Preparation of binary mixtures (Brexpiprazole +Aripiprazole) for calibration set and validation set

Appropriate and accurate volume aliquots of the stock solutions were taken according to following binary mixture scheme and volume made up to 10 ml with methanol.
The absorbance data matrix was obtained by measuring the absorbance at each wavelength points (240-350 nm) in spectral region between 200-400nm.
25 sets are taken for calibration set and for validation set.

Calibration set
A set of 18 mixtures was prepared in methanol, applying a multilevel multifactor design in which two levels of concentrations of Brexpiprazole and Aripiprazole within the stated range were introduced as shown in Table-1.

Validation set
A set of 7 mixtures was prepared in methanol, applying a multilevel multifactor design in which two levels of concentrations of Brexpiprazole and Aripiprazole within the stated range were introduced as shown in Table-2.

Table 1: Calibration set

Sr.no	Brexpiprazole (mcg/ml)	Aripiprazole (mcg/ml)
1	5	10
2	1	15
3	5	15
4	2	20
5	3	15
6	1	5
7	3	5
8	5	5
9	5	25
10	4	5
11	2	5
12	4	15
13	4	25
14	4	20
15	2	25
16	3	25
17	1	20
18	2	15

Table 2: Validation set

Sr.no	Brexpiprazole (mcg/ml)	Aripiprazole (mcg/ml)
1	3	20
2	2	10
3	4	10
4	5	20
5	1	25
6	1	10
7	3	10

Producing Absorbance matrix A
Absorbance matrix A was produced by measuring absorbance at 23 wavelengths in the spectrum region between the 240-350 nm. This region was selected because it contained most relevant information about both the drugs. The spectra of prepared binary mixture standard were recorded in the range of 240-350 nm. Absorbance values in this wavelength region were recorded.

1. Classical least squares (CLS) method
The mathematical model for this method can be represented by A=CK where A is m×n matrix of calibration spectra, C is m×l matrix of component spectra and K is l×n matrix of absorptivity at unit concentration and unit pathlengh. (m=18,l=2,n=23). The Calibration coefficient matrix (K) was calculated as K=pinv (C)*A and using the K value of calibration coefficient unknown was computed using formula C=A*pinv(K).

Computing the K (calibration coefficient) Matrix
The value of calibration coefficient can be calculated by using following equation:

$$K=pinv(C)*A$$

Table 3: K-Matrix

Sr.no	Wavelength	Brexpiprazole	Aripiprazole
1	240	0.0719	0.0127
2	245	0.0617	0.0140
3	250	0.0629	0.0163
4	255	0.0655	0.0175
5	260	0.0642	0.0165
6	265	0.0576	0.0138
7	270	0.0507	0.0104
8	275	0.0455	0.0078
9	280	0.0418	0.0067
10	285	0.0379	0.0064
11	290	0.0330	0.0057
12	295	0.0306	0.0050
13	300	0.0240	0.0021
14	305	0.0236	0.0011
15	310	0.0269	0.0009
16	315	0.0273	0.0008
17	320	0.0279	0.0007
18	325	0.0320	0.0009
19	330	0.0251	0.0005
20	335	0.0216	0.0004
21	340	0.0249	0.0006
22	345	0.0126	0.0000
23	350	0.0024	-0.0003

Predicting the unknown concentration
Spectra of solution containing unknown concentration of Brexpiprazole and Aripiprazole were recorded in the range of 200-400 nm and absorbance matrix A was generated. Using the calibration coefficient matrix K, the concentration was computed using following equation:

$$C=A*pinv(K)$$

2. Inverse least squares (ILS) method
The mathematical model for this method can be represented by C=AP where P is l×n matrix of unknown calibration, C and A are same as defined for CLS method mentioned above at unit concentration and unit path length. (m=18,l=2,n=23) The calibration coefficient matrix (P) was calculated as P=pinv (A)*C and using the P value of calibration coefficient unknown was computed using formula C=A*P.

Computing the P (calibration coefficient) Matrix
The value of calibration coefficient can be calculated by using following equation:

$$P=pinv(A)*C$$

Table 4: P-Matrix

Sr.no	Wavelength	Brexpiprazole	Aripiprazole
1	240	-0.2090	1.4996
2	245	-0.0123	0.5127
3	250	-0.5390	-3.9798

4	255	0.4082	4.8474
5	260	0.1865	-7.7676
6	265	0.8695	2.6569
7	270	-0.4797	7.3912
8	275	0.7782	-1.0558
9	280	-0.4701	-4.2544
10	285	0.7782	4.2599
11	290	-0.4701	2.3385
12	295	-0.6254	-5.3948
13	300	-1.0812	2.6232
14	305	-0.2834	7.8943
15	310	0.9381	-3.6731
16	315	1.1888	-1.6387
17	320	-0.2559	-9.3896
18	325	0.0483	1.4445
19	330	-0.3669	4.9663
20	335	1.4999	-3.8014
21	340	-1.4519	5.1712
22	345	-0.0274	-6.9977
23	350	0.5717	2.9441

Predicting the unknown concentration

Spectra of solution containing unknown concentration of Brexpiprazole and Aripiprazole were recorded in the range of 200-400 nm and absorbance matrix A was generated. Using the calibration coefficient matrix P, the concentration was computed using following equation:

$$C=A*P.$$

3. Principal component regression (PCR) method

PCR is the method which works on the principal of reducing the dimensionality of the original data. Absorbance matrix and concentration matrix as shown above were generated and data was fed to software. The absorbance matrix (X) used for calibration contains total 23 variables i.e. wavelengths at which absorbance values are measured. PCR will compute a few PCs and will perform regression of these PCs with concentration (Y). The algorithm used for PCR was NIPALS i.e. nonlinear iterative partial least squares. Validation was set as full cross validation. The data of absorbance values at 23 wavelengths were used as X space (predictors) and the data containing concentration of ARP and LMG in 18 calibration standards were used as Y space (responses).

Determining optimum number of principal components for PCR

Three major parameters are considered for determination of number of PCs to be taken into account.

1. Total explained Y variance
2. Total residual Y variance
3. Root Mean Square of Prediction values for validation

(Concentrations are Y space-the responses; and absorbance values at different wavelengths are considered as X space-the predictors. Mixtures prepared as calibration standards may be referred to as samples.)

The model should have as low residual variance as possible. This means that the model should explain most of the variance in the data i.e. explained variance should approach 100%. For this, number of PCs should be optimized. Normally, first 2-3 PCs will explain nearly (not exactly) 100% of variance in data. Moreover, the model should have as low RMSEP values as possible.

The software can validate the model by full cross validation method, where one sample from the calibration set is left out each time and model are calibrated using remaining samples. Then the prediction is made for left out sample and its residual are calculated. The same process is repeated until each sample is left out once. So, there were total 18 segments for validation, because there were 18 calibration standards or samples. Finally, one can view the plot of residual variance or explained variance (for calibration and validation both) or RMSEP vs. number of PCs. This can help in determining the optimum number of PCs.

Once the model is calibrated with optimum number of PCs, the model can predict the unknown concentration from its absorbance data. Maximum number of PCs was fixed to 7.

4. Partial least squares or projection to latent structures (PLS) method

PLS computes factors for X and Y both and then correlates them. It models both the X-and Y-matrices simultaneously to find the latent variables in X that will best predict the latent variables in Y. Full cross validation method is used for determining the optimum number of factors. The algorithm used for PLS was NIPALS i.e. nonlinear iterative partial least squares.

Determining optimum number of principal components for PLS

The number of factors to be taken into account was determined by full cross validation method and following parameters were considered:

1. Total explained Y variance
2. Total residual Y variance
3. RMSEP values for validation

Results and Discussion

The chemical structures of Brexpiprazole and Aripiprazole are shown in Figure 1 and Figure 2 Respectively. Figure 3 shows the UV spectra of these drugs and the mixture of them. As this figure shows there is clear overlapping between them. The spectral overlapping of these drugs prevents resolution of the mixtures by direct spectrophotometric measurements.

Single component calibration

To find the linear, dynamic range of each component, calibration graphs were obtained. The absorption spectra were recorded over 200-400nm against a methanol blank. The

linear range for each drug was determined by plotting the absorbance as its λmax (Brexpiprazole at 325nm and Aripiprazole at 255nm) versus the sample concentration. The calibration curves were linear between 1-5mcg/ml of Brexpiprazole and 5-25mcg/ml of Aripiprazole. The characteristic parameters for the regression equations of individual calibration by absorption of UV spectra are shown in Table-5.

Table 5: Single component linear regression analysis

Sr.no	Compound	Regression Equation	R^2	SD of the slope	SD of the intercept
1	Brexpiprazole	Y=0.075X+0.012	0.998	0.00041	0.02663
2	Aripiprazole	Y=0.121X-0.0031	0.999	0.00084	0.00132

Multivariate Methods

The First step in multivariate methods involved constructing the calibration matrix. The wavelength range used was 240-350nm. 23 spectral points with 5nm intervals were selected within this range. The composition of the calibration mixtures were randomly designed in order to collect maximum information from the spectra of these mixtures.

The quality of multicomponent analysis is dependent on the wavelength range and spectral mode used. The UV absorption spectra of Brexpiprazole, Aripiprazole and the mixture at their nominal concentrations are shown in Figure-3.The calibration set and validation set were randomly prepared with the mixture of Brexpiprazole and Aripiprazole in methanol. (Table 1 & Table 2 Respectively). The UV spectra were observed in the region between 200-400nm and the absorbance were measured at 23 wavelengths points in the region between 240-350 nm with 5nm intervals.

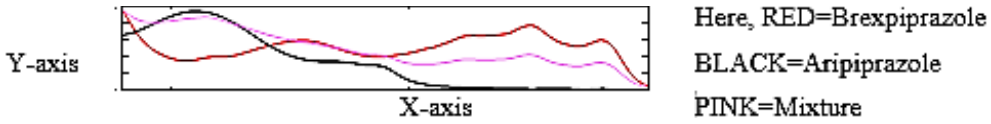


Fig 3: Overlay spectra of brexpiprazole, aripiprazole and mixture

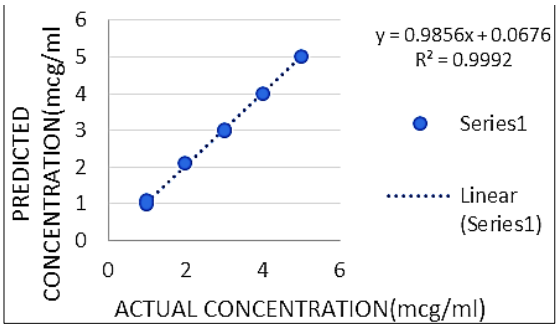
Here, Y-axis=Absorbance & X-axis=Concentration

Validation of CLS, ILS, PCR and PLS Methods

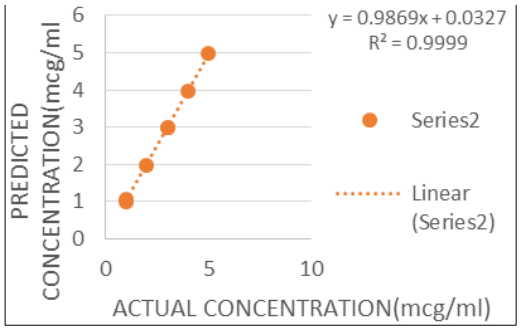
The validation set Prepared as described in Table-2 was subjected to analysis by developed models of all the four methods. Though The PCR and PLS models are validated using full cross validation, these methods are also applied to validation set.

Predicted vs Actual concentration plot

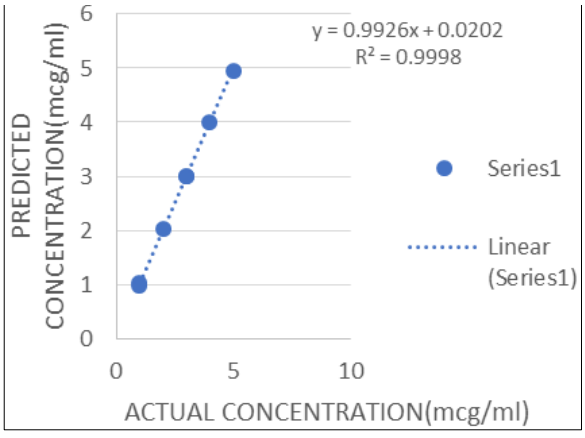
Predicted concentration of validation samples were plotted against the actual concentration values. This tool is used to determine whether the model accounts for concentration variation in the validation set or not. Plots were expected to fall on straight line with slope of 1 and o intercept. The predicted vs actual concentration plots of prepared validation samples are shown in Figure-4 for Brexpiprazole and Figure-5 for Aripiprazole. It was noticed that Brexpiprazole and Aripiprazole samples lay on straight line and the equations of these lines are shown on the graph. This indicates that the prediction ability of the validation set is very much better in terms of recovery.



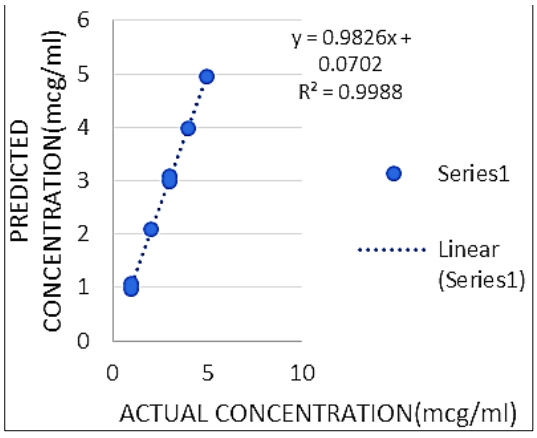
1. Brexpiprazole CLS Graph



2. Brexpiprazole ILS Graph



3. Brexpiprazole PCR Graph



4. Brexpiprazole PLS Graph

Fig 4: Brexpiprazole Predicted vs actual concentration for CLS, ILS, PCR AND PLS

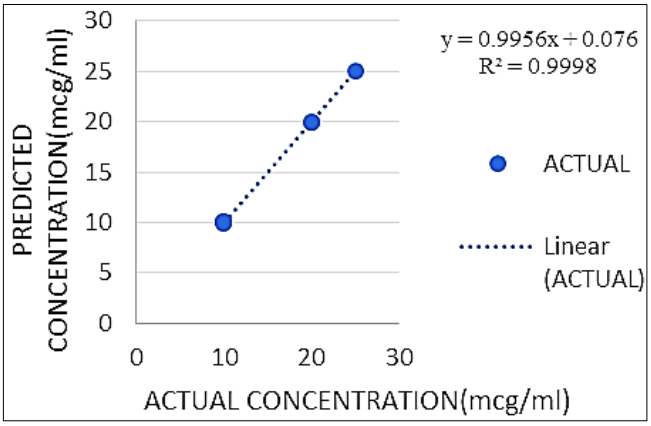
Principal component regression (PCR) and partial least squares or projection to latent structures (PLS)

The PCR and PLS models were developed by the unscrambler X program. Model development was performed by using calibration standards.

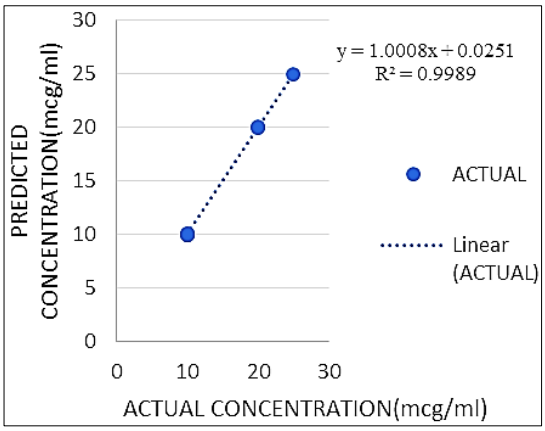
Leave-one-out cross validation (LOO-CV) was used to validate the PCR and PLS models in model development and obtain optimum latent variables (number of factor) of the model. To select the optimum latent variables in the PLS and PCR algorithms, a cross-validation method, leaving out one sample at a time, was employed using 18 calibration spectra.

The predicted concentrations of the components in each sample were compared with the actual concentrations of the components in each of the validation samples and the root mean square error of cross validation (RMSECV) was calculated for each method. The RMSECV was used as a diagnostic test for examining the error in the predicted concentrations. This is shown in Table-6.

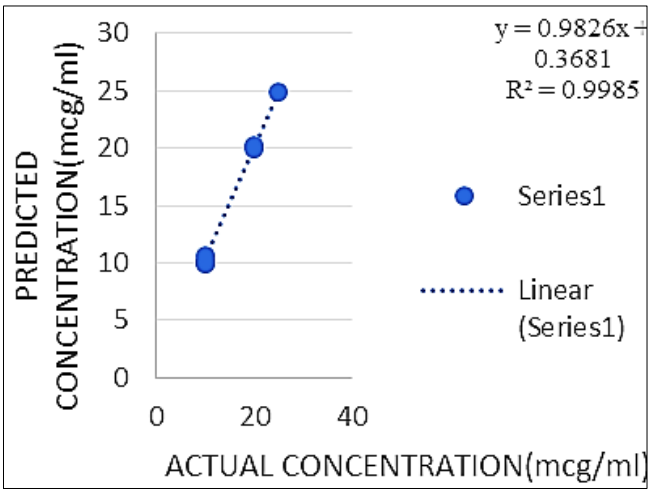
The model is the key to achieving the correct quantitation in PLS and PCR calibrations. The evaluation of the predictive abilities of the models was performed by plotting the actual known concentration against the predicted concentrations and the plots are mentioned in Figure-4 and Figure-5.As observed, there was good agreement between the predicted(calculated) and actual concentration of the drugs. Satisfactory correlation coefficient (R^2) values were obtained for each compound in the validation set by PCR and PLS optimized models indicating good predictive abilities of the models.



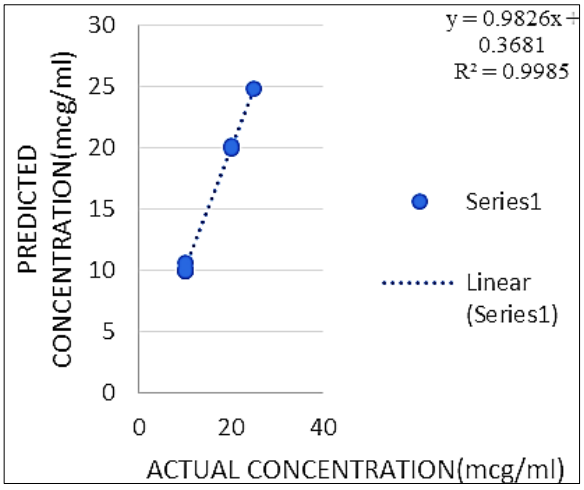
1. Aripiprazole CLS Graph



2. Aripiprazole PCR Graph



3. Aripiprazole ILS Graph



4.Aripiprazole PLS Graph

Fig 5: Aripiprazole predicted vs actual concentration for CLS, ILS, PCR AND PLS

In PCR, It can be observed that as the number of PC increases, explained variance in Y increases and RMSEP decreases. 2 PCs gave satisfactory results in terms of explained variance, residual variance and RMSEP. Thus, 2 PCs were selected for prediction. The concentrations of validation set were successfully predicted. Effect of number of PCs on Explained Y-variance (PCR)-should be high (Near To 100) Effect of number of PCs on Residual variance (PCR)-should be low (Near to Zero).

In PLS, It can be observed that as the number of PC increases, explained variance in Y increases and RMSEP decreases. 2 PCs gave satisfactory results in terms of explained variance, residual variance and RMSEP. Thus, 2 PCs were selected for prediction. The concentrations of validation set were successfully predicted. Effect of number of PCs on Explained Y-variance (PCR)-should be high (Near To 100) Effect of number of PCs on Residual variance (PCR)-should be low (Near to Zero).

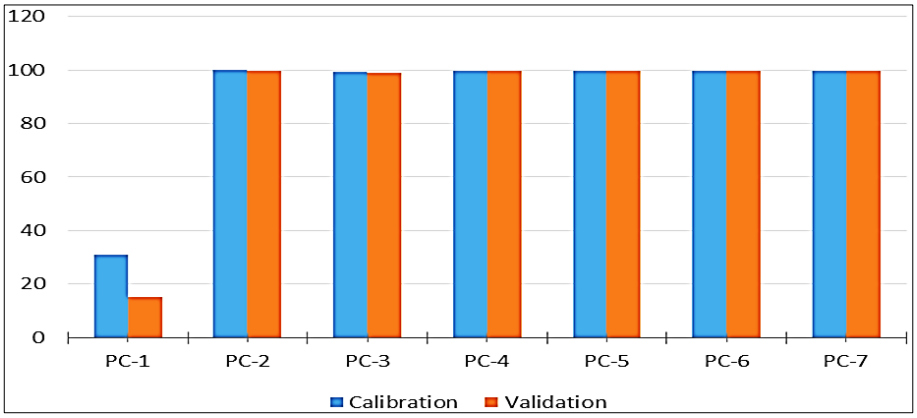


Fig 6: Effect of number of PCs on explained Y variance.

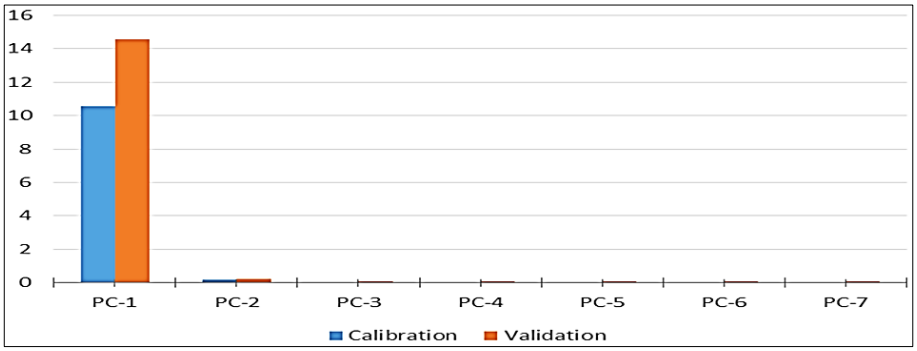


Fig 7: Effect of number of PCs on residual Y variance

Root mean square error of prediction (RMSEP)

The predictive ability of the model can be defined as RMSEP.RMSEP summarizes both precision and accuracy. It is used for examining the errors in the predicted concentrations. The results of future predictions can then be presented as "predicted values ±2*RMSEP".

Applicability of the developed Chemometric methods

All four methods were successfully applied for the estimation of Brexpiprazole and Aripiprazole in simulated mixture. Results are tabulated below:-Table-7.

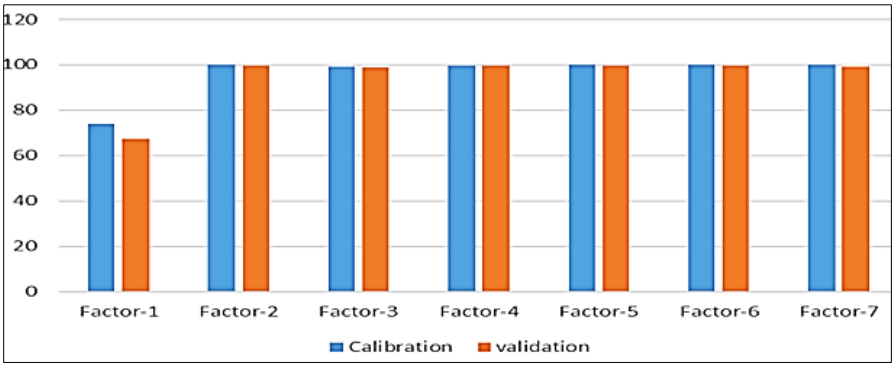


Fig 8: Effect of number of factors on explained Y variance

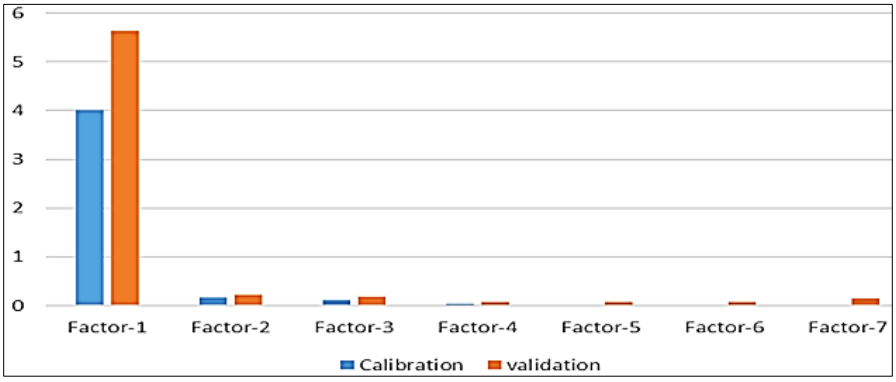


Fig 9: Effect of number of factors on residual Y variance

Table 7: Applicability of Proposed Methods

Sr.no	Method	Brexpiprazole*	Aripiprazole*
1	CLS	99.97 ± 0.164	100.05 ± 0.0654
2	ILS	99.12 ± 1.185	99.62 ± 1.261
3	PCR	100.01 ± 0.0021	100.61 ± 0.0109
4	PLS	100.04 ± 0.0041	100.28 ± 0.0218

*Average ± SD (n=3) of three experiment

Table 6: Obtained statistical values for the simultaneous analysis of brexpiprazole and Aripiprazole multivariate calibration methods (CLS, ILS, PCR &PLS)

Sr.no	Parameter	Brexpiprazole				Aripiprazole			
		CLS	ILS	PCR	PLS	CLS	ILS	PCR	PLS
1	Concentration range	1-5 mcg/ml				5-25 mcg/ml			
2	Spectral region(nm)	240-350 nm				240-350nm			
Cross-validation result									
3	Optimum number of factors	-	-	4	5	-	-	4	6
4	slope	0.985	0.986	0.992	0.982	0.995	1.000	0.982	0.982
5	intercept	0.067	0.032	0.020	0.070	0.076	0.025	0.368	0.368
6	R^2	0.999	0.999	0.999	0.998	0.999	0.998	0.998	0.998
7	RMSE-CV(mcg/ml)	-	-	0.368	0.411	-	-	2.728	3.687
8	RMSEC	0.244	0.262	0.737	0.764	2.333	2.904	2.638	2.831
9	RMSEP	0.609	0.305	5.298	2.897	0.207	0.201	2.761	5.127
10	SEC	0.703	0.523	-	-	0.879	0.265	-	-
Validation Result									
11	Slope	1.013	1.001	1.002	1.010	1.007	0.995	1.213	0.992
12	C.I. of slope	0.095 1.365	0.087 1.276	0.096 1.381	0.079 1.172	0.096 1.261	0.763 1.171	0.921 1.491	0.691 1.201
13	intercept	0.854	0.183	0.002	0.018	0.023	0.065	0.396	0.671
14	C.I. of intercept	0.712 0.981	0.982 0.381	0.001 0.004	0.005 0.092	0.009 0.098	0.008 0.101	0.109 0.587	0.341 0.981
15	Standard error	0.004	0.184	0.753	0.009	0.342	0.514	0.693	0.531
16	R^2	0.999	0.995	0.998	0.999	0.996	0.999	0.997	0.999
17	RMSEC	3.882	0.542	0.871	0.294	2.651	1.984	0.261	0.186

Here,
RMSECV=Root Mean Square Error of Cross-Validation
RMSEC= Root Mean Square Error of Calibration
RMSEP=Root Mean Square Error of Prediction
SEC=Standard Error of Calibration
C.I. = Confidence Internal

Conclusion

The main goal of the proposed work is to develop and validate the novel chemometrics-assisted algorithm for the simultaneous determination of Brexpiprazole and Aripiprazole in pharmaceuticals via chemometrics-assisted spectrophotometry method. According to the obtained data, four different chemometrics algorithm exhibited good accuracy and their correlation matrixes showed that there is no difference between each algorithm. Thus, each of them could be confidently used in the simultaneous de- termination of those pharmaceuticals. These proposed method presents a good alternative to chromatographic separations in routine quality control samples without using mobile phase or any other separation apparatus. Generally, chemometrics methods are very convenient techniques for the simultaneous analysis of multiple compounds in which the overlap of the spectra of the active compounds creates an interference that makes it impossible to determine the concentrations of each compound via classical linear regression equations. Correlation matrix confirmed that each method has a very small difference and the prediction power of PLS and PCR is relatively better. Another advantage of the proposed method is that all analysis was performed neither derivatization nor ratio spectra modes which are ex- pensive and time-consuming steps. Besides, the simplicity of the chemometric calibration methods comes from the ability to evaluate a huge amount of samples in a short time as accurately and precisely in comparison with chromatographic methods. The obtained results demonstrated that the proposed spectrophotometric method can be applicable as a possible alternative method for the simultaneous determination of Brexpiprazole and Aripiprazole in the routine quality control analysis of pharmaceutical industries

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