Research Article

Chemometric Assisted Spectrophotometric Method Development for Evaluation of Torsemide and Eplerenone in their Combined Tablet Dosage Forms

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ABSTRACT

Aim: In a present work two drugs Torsemide and Eplerenone were estimated from their combined tablet dosage forms by applying chemometric assisted spectrophotometric method. **Methods:** The methods are based on chemometrics a (multivariate) method which includes classical least square (CLS) and inverse least square (ILS). These methods were employed for simultaneous determination of Torsemide and Eplerenone in tablet dosage forms without any prior separation of components. For these methods the overlapping spectra of two drugs not subjected any conversions. The data processing of chemometric was accomplished by using software named Chemometrics Toolbox 3.02 which is associated with MATLAB 6 and excel. **Results:** The results obtained from CLS and ILS methods were compared statistically. These chemometric methods were applied for the determination of these two drugs in their marketed tablet dosage form without any prior separation procedure of the drugs. The mean percent recoveries and values of relative standard deviation for these two methods were found to be 99.72/0.536 for Torsemide and 100.06/0.384 for Eplerenone. **Conclusion:** The two chemometric methods developed can be successfully applied for the quantitative estimation of drugs from their dosage form.

Key words: Spectrophotometry, Chemometrics, Torsemide, Eplerenone, Classical least square method, Inverse least square method, Root mean square error of prediction

INTRODUCTION

The chemometric methods are useful for analysis of multi-component by the resolving their complicated spectra from mixtures of drugs.[1] The chemometric methods of analysis have utilizations and excellence over traditional analytical methods for example; the mixtures of components can be appropriately estimated without separating drugs from their mixture. Other advantages are; these methods are easy in application, sensitive to smallest concentration, useful and economical in comparison to other methods of analysis used for simultaneous determination of components in multicomponent mixtures. These methods are more advantageous because while performing the calibration and analysis of drugs the concentration of other components are not interfering and also the determination of components in a mixture becomes rapid.[2]

Torsemide (TOR) is from loop diuretic category[3,4] and chemically it is 3-Pyridinesulfonamide, N- [[(1 methylethyl) amino] carbonyl]-4-[(3-methylphenyl) amino]-1-Isopropyl- 3-[(4-m-toluidino-3-pyridyl) sulfonyl] urea[5] (Figure 1). This drug is indicated in the treatment of hypertension or edema associated with congestive heart failure, renal disease and hepatic disease.

The chemical name of Eplerenone (EPL) is methyl (1'R,2R,2'S,9'R,10'R, 11'S,15'S,17'R)-2',15'-dimethyl-5,5'-dioxo-18'-oxaspiro[oxolane-2,14' pentacyclo[8.8.0.0^{1},^{17}.0^{2}, ^{7}.0^{11},^{15}] octadecan]- 6'-ene-9'- carboxylate[6] (Figure 2). This drug is from Steroid

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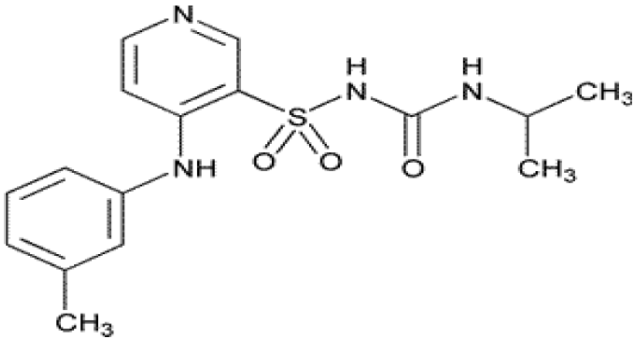

Figure 1: Structure of Torsemide.

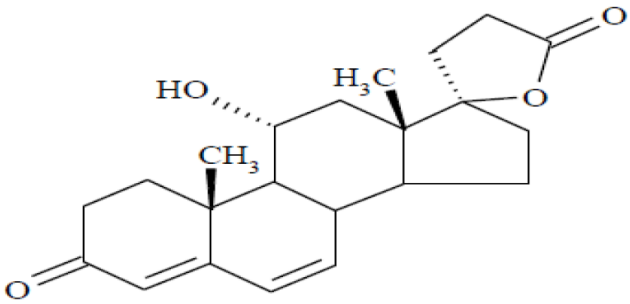

Figure 2: Structure of Eplerenone.

Lactones class, and use in treatment of Edema associated with Congestive Heart Failure. Eplerenone is act by reducing the activity of aldosterone and used with other drugs in the management of chronic heart failure. It is used as antihypertensive agent and diuretic.[3,4]

Torsemide is official in USP 2007,[7] and Eplerenone are official in IP 2014,[8] and both the drugs are analysed by Liquid chromatographic method.

After extensive literature review we found that several analytical methods were reported for the determination of Torsemide and Eplerenone in single dosage forms and in combination with other drugs. The different methods are high performance liquid chromatography (HPLC),[9-19] TLC and HPTLC,[20,21] HPLC LC-MS,[22,23] and spectrophotometry.[24-27] Some UV spectrophotometric and HPLC methods,[28-30] are reported for the determination of Torsemide and Eplerenone in combined tablet dosage forms. In this paper, we have reported the investigation and development of rapid analytical method for the simultaneous determination of Torsemide and Eplerenone. The methods are based on UV spectrophotometry, and the resulting overlapping spectra of drugs are processed by chemometrics. The application of chemometrics allows the interpretation of multivariate data and is very useful for the simultaneous determination of the organic components. In the present study, the two chemometric methods are successfully used for the simultaneous estimation of Torsemide and Eplerenone.

MATERIALS AND METHODS

Commercial tablets Planep-T containing 10 mg of Torsemide and 25 mg of Eplerenone were taken for analysis. The spectrophotometric analysis of mixture of two drugs was carried out by using a Shimadzu UV-Vis double beam spectrophotometer which is equipped with 1 cm quartz cells and connected to computer with UV Probe Version 2.10 software. The CLS and ILS calculations were performed in Chemometrics Toolbox 3.02 software in connection with MATLAB R2015a Software and Excel.

Preparation of standard solutions and calibration

The two drugs were measured by using spectrophotometer. The stock solution of 1000 µg/ml of TOR and EPL were prepared by dissolving 10 mg of each drug in 10 ml of methanol. Further dilutions were made in methanol to obtain concentrations ranging from 3-10µg/ml for TOR and 7.5-25µg/ml for EPL and their different synthetic mixtures were prepared by using the stock solutions. The zero order spectra were recorded over the wavelength range 200-400 nm against the solvent blank.

Preparation of binary mixtures of TOR and EPL

The binary mixtures of two drugs were prepared from the above stock solutions. The calibration set of 15 different standard solutions and validation set of 10 mixed standard solutions containing the concentrations with different quantities of TOR and EPL was prepared. The concentrations of mixed standards fall in the linearity range of two drugs. The solutions of calibration set and validation set were scanned in spectrophotometer. The absorbance data matrix was generated by measuring the absorbance at 31 wavelength points with the interval of 2 nm between 240 to 300 nm in spectral region. A calibration set of 15 different mixtures was prepared by using methanol as solvent and a multilevel multifactor design was used, for these design concentrations of TOR and EPL were taken at two different levels. Similarly a validation set of 10 different mixtures was prepared and multilevel multifactor design was applied to the concentrations of TOR and EPL at two different levels. The composition of calibration set and validation set are shown in Table 1 and Table 2.

Table 1: Composition of Calibration set for two constituents used in CLS and ILS techniques.

Mix. No.	TOR (µg/ml)	EPL (µg/ml)
1	3	15
2	3	20
3	3	25
4	4	7.5
5	4	10
6	4	25
7	6	10
8	6	15
9	6	20
10	8	7.5
11	8	20
12	8	25
13	10	7.5
14	10	10
15	10	15

Table 2: Composition of Validation set for all two constituents used in CLS and ILS techniques.

Mix. No.	TOR (µg/ml)	EPL (µg/ml)
1	3	7.5
2	3	10
3	4	15
4	4	20
5	6	25
6	6	7.5
7	8	10
8	8	15
9	10	20
10	10	25

Preparation of sample solutions

For performing assay, twenty tablets of brand (Planep-T) were weighed and powdered by using the mortar and pestle. An amount of the powder equivalent to 25 mg of EPL was weighed accurately and taken in a 25 ml calibrated volumetric flask and dissolved in methanol. The solution was sonicated and filtered by using Whatman filter paper number 41. The filtered solution was diluted up to 25 ml with methanol. The resulting solution was further diluted with methanol of the concentration falling within calibration range. After scanning in spectrophotometer, the proposed chemometric (CLS and ILS) methods were used for determination of sample solutions.

Classical least squares method

In CLS method linear relationship between the absorbance and the concentrations of components at each wavelength were used for calculation. In this method matrix notation was formed on the basis of Beer's law model for m calibration standard solutions which contains l chemical components with spectra of n, computed absorbance is expressed by the following equation,[1,2]

$$A = C \times K + EA \quad (1)$$

where A is the $m \times n$ matrix of calibration spectra, C is the $m \times l$ matrix concentrations of component, K is the $l \times n$ matrix of proportionality constants absorbance-concentration relation and EA is the $m \times n$ matrix of spectral errors or residuals which are not fitted in the model.

Inverse least squares (ILS) method

The ILS method measures concentration in relation to absorbance. It consists of the inverse of Beer's law model for m calibration standards solutions with spectra of n computed absorbance is given by the following equation,[1,2]

$$C=A\times P+Ec \quad (2)$$

Where C and A are concentration and Absorbance as mentioned in CLS method, P is matrix of $n \times l$ and depends upon calibration co-efficient of samples which are obtained from their concentrations at typical spectral intensities and Ec is vector of errors and designated by $m \times l$.

Since in ILS method the number of wavelengths should not be more than the total number of calibration mixtures, the wavelengths for measurement were selected on basis of multiple linear regressions.

RESULTS AND DISCUSSION

Figure 3 shows the zero-order overlay spectra of TOR and EPL as well as their corresponding binary mixture in methanol. As depicted in Figure 3, the spectra of TOR and EPL are overlapped with each other. Estimation of these drugs by using simple spectrophotometric method becomes difficult; to solve this problem chemometric method can be used to determine the two compounds individually from their mixtures. To estimate the drugs in condition of overlapped spectra the chemometric calibrations methods can be used.

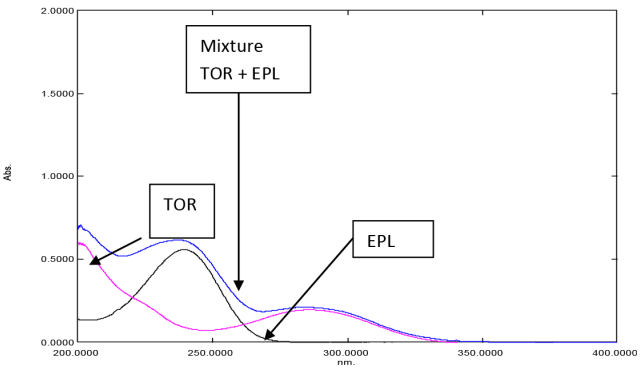

Figure 3: Overlain spectra of TOR (10 *µg*/ml), EPL (25 *µg*/ml) and mixture.

Multivariate calibration in CLS and ILS method

The calibration set was prepared consisting 15 standard mixture solutions containing the different concentrations of TOR and EPL selected randomly falling within the linearity range of two drugs. The absorbances of the prepared solutions were measured in the spectral region of 240-300 nm at interval of 2 nm and absorbance data was generated. The chemometric calibrations were performed by using the CLS and ILS algorithms and correlation between concentrations and its absorbance data. The results obtained from these methods of multi-component analysis are depend upon the wavelength range selected, concentration of solutions of calibration set, calibration range and spectral mode used. In the CLS technique full spectrum of drugs is computed, therefore selection of wavelength is not important as all available wavelengths are used for estimation. While in ILS method the frequencies were selected on the basis of multiple linear regressions.

CLS Method

For estimation of drugs by CLS method by using the coefficient matrix (K). The coefficient matrix can be calculated from linear equation obtained by plotting the absorbance data and concentration of solutions of calibration set. The coefficient matrix (K) replaced in the linear equation system and the calibration of CLS can be presented as follow:

$$\begin{bmatrix} C_{TOR} \\ C_{EPL} \end{bmatrix} = \begin{bmatrix} 0.0252 & 0.0241 & 0.0232 & 0.0227 & 0.0225 & 0.0224 \\ 0.0225 & 0.0229 & 0.0236 & 0.0244 & 0.0255 & 0.0268 \\ 0.0283 & 0.0299 & 0.0360 & 0.0357 & 0.0347 & 0.0328 \\ 0.0303 & 0.0273 & 0.0239 & 0.0203 & 0.0169 & 0.0135 \\ 0.0105 & 0.0079 & 0.0058 & 0.0041 & 0.0316 & 0.0334 \\ 0.0352 & 0.0369 & 0.0384 & 0.0398 & 0.0409 & 0.0417 \\ 0.0422 & 0.0425 & 0.0425 & 0.0423 & 0.0444 & 0.0411 \\ 0.0029 & 0.0021 & 0.0015 & 0.0011 & 0.0008 & 0.0007 \\ 0.0006 & 0.0005 & 0.0004 & 0.0004 & 0.0004 & 0.0004 \\ -0.0003 & 0.0003 & 0.0401 & 0.0390 & 0.0376 & 0.0003 \\ 0.0003 & 0.0003 & & & & \end{bmatrix} \times \begin{bmatrix} A1 & A16 \\ A2 & A17 \\ A3 & A18 \\ A4 & A19 \\ A5 & A20 \\ A6 & A21 \\ A7 & A22 \\ A8 & A23 \\ A9 & A24 \\ A10 & A25 \\ A11 & A26 \\ A12 & A27 \\ A13 & A28 \\ A14 & A29 \\ A15 & A30 \\ & A31 \end{bmatrix}$$

ILS method

In ILS method, the coefficient matrix (P) was used for estimation of drugs which can be determined from the linear equation by plotting the absorbance against the concentration of solutions of calibration set. From the linear equation system the value of (P) was replaced and calibration for ILS was obtained as given below:

$$\begin{bmatrix} C_{TOR} \\ C_{EPL} \end{bmatrix} = \begin{bmatrix} 0.0091 & 0.3044 & 0.0049 & -0.7485 & 0.0427 & 3.0777 & -0.0164 \\ -1.4775 & -0.0057 & -1.7688 & -0.1025 & -1.0110 & -0.0059 & 1.3055 \\ 0.1697 & 0.5379 & -0.0363 & 0.7841 & -0.1050 & -0.5824 & 0.0455 \\ -0.6725 & -0.0732 & -1.3216 & 0.0846 & 3.0272 & -0.0264 & -1.6172 \\ -0.0941 & -0.1683 & 0.0654 & -0.4711 & 0.1097 & -0.8041 & 0.0120 \\ 0.5721 & -0.0743 & 1.1343 & 0.1236 & 0.7115 & -0.1064 & 0.0270 \\ -0.1164 & 0.0196 & -0.2456 & 0.6984 & 0.1300 & -0.2178 & 0.1773 \\ 0.6230 & 0.1787 & -1.0136 & 0.0063 & 0.0132 & -0.1109 & -1.2856 \\ -0.1143 & -2.5322 & -0.0698 & -0.1053 & 0.1667 & 2.9949 & \end{bmatrix} \times \begin{bmatrix} A1 & A16 \\ A2 & A17 \\ A3 & A18 \\ A4 & A19 \\ A5 & A20 \\ A6 & A21 \\ A7 & A22 \\ A8 & A23 \\ A9 & A24 \\ A10 & A25 \\ A11 & A26 \\ A12 & A27 \\ A13 & A28 \\ A14 & A29 \\ A15 & A30 \\ & A31 \end{bmatrix}$$

Statistical parameter

The regression model can be applied predictively and described in different ways. The chemometric methods are expressed in terms of SEP stands for standard error of prediction and SEC stands for standard error of calibration or root mean square error of prediction is expressed by formula given below;

$$RMSEP = \sqrt{\frac{\sum_{i=1}^{N} (C_i^{added} - C_i^{found})^2}{n}}$$

In above equation, *C* is predicted concentration of TOR and EPL in mixture and n is the total number of the mixtures prepared of both drugs.

The RMSEP were calculated by application of CLS and ILS methods to the validation set of the mixtures of both drugs and the results are mentioned in Table 3.

The validity of the calibration methods can be determined by estimating the two drugs simultaneously from their validation set. The result of the mean percent recovery for CLS and ILS methods for the mixed solutions of two drugs was found to be in acceptable limit. The recovery study was carried out by addition of known amounts of standard drugs to a fixed concentration of the tablet formulations. A fixed volume or concentration of the sample solution was taken and then a known volume

Table 3: Statistical parameters obtained for CLS and ILS methods.

Drugs	RMSEP (CLS)	RMSEP (ILS)
Torsemide	0.06069	0.05097
Eplerenone	0.05097	0.58312

Table 4: Results of Recovery study by CLS method.

Torsemide			Eplerenone		
Added (µg/ml)	Found (µg/ml)	% Recovery	Added (µg/ml)	Found (µg/ml)	% Recovery
3	3.0401	101.34	7.5	7.4914	99.89
3	2.9532	98.44	10	9.9842	99.84
4	4.0152	100.38	15	14.9025	99.35
4	4.0296	100.74	20	19.7630	98.82
6	5.9707	99.51	25	25.3326	101.33
6	6.0932	101.55	7.5	7.4829	99.77
8	7.9642	99.55	10	9.8795	98.80
8	7.9611	99.51	15	14.8325	98.88
10	9.8934	98.93	20	19.7562	98.78
10	9.8965	98.97	25	24.7411	98.96
Mean Recovery		99.89	Mean Recovery		99.44
%RSD		0.7162	%RSD		0.4173

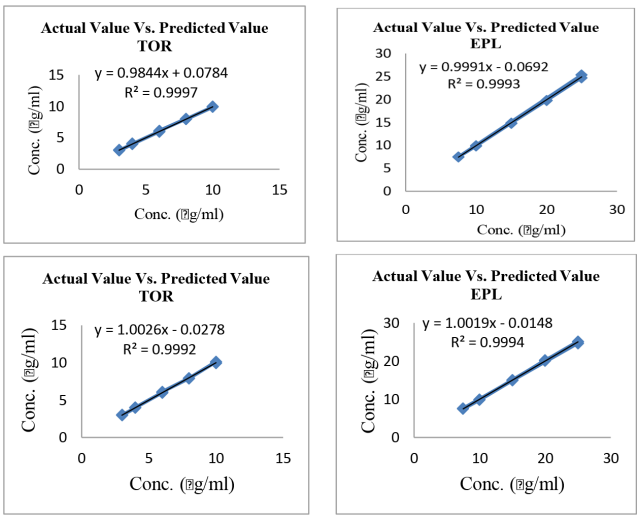

Figure 4: CLS – Expected vs. Predicted Concentration of TOR and EPL, ILS – Expected Vs. Predicted Concentration of TOR and EPL.

Table 5: Results of Recovery study by ILS method.

Torsemide			Eplerenone		
Added (µg/ml)	Found (µg/ml)	% Recovery	Added (µg/ml)	Found (µg/ml)	% Recovery
3	2.9485	98.28	7.5	7.5161	100.21
3	2.9968	99.89	10	9.8957	98.96
4	3.9726	99.32	15	14.9995	100.01
4	4.0048	100.12	20	20.2427	101.21
6	5.9682	99.47	25	24.6914	98.77
6	6.1031	101.72	7.5	7.5727	100.97
8	7.8929	98.66	10	9.8767	98.77
8	7.9193	98.99	15	15.0481	100.32
10	10.1278	101.28	20	20.1609	100.80
10	9.9513	99.51	25	25.1457	100.58
Mean Recovery		99.72	Mean Recovery		100.06
%RSD		0.5367	%RSD		0.3849

*Mean of three individual determinations

of working standard solutions was spiked. Finally the volume in volumetric flask was adjusted with methanol and mixed. Then the resulting mixture solutions were analyzed and recoveries of both drugs in chemometric methods were assessed. The results obtained were found to be closer to expected values. The mean of percentage recoveries and RSD values of the mentioned methods were calculated and are depicted in Table 4 and 5. The result of recovery study was closer to 100% and RSD was found to be less than 2 which indicate that the methods were validated successfully. The result also indicates that the proposed methods are accurate and excipients are not interfering in estimation of two drugs. The linearity of the proposed chemometric method for determination of TOR and EPL was assessed by analysing a series of different concentrations of standard drug. The linearity for both the methods were determined by taking different concentrations of two drugs and was found to be range of 3-10µg/ml for TOR and 7.5-25µg/ml for EPL. Linearity was performed repeatedly thrice.

The methods involve the comparison between predicted concentrations of the drugs in all sample mixture solutions and the actual concentrations taken of the drugs in all mixture solutions of validation set. On the basis of this comparison the root mean square error of cross validation (RMSECV) was computed for both the methods. The error in the predicted concentrations can be estimated from the values of RMSECV. The model is very important for quantitation of drugs by CLS and ILS calibration methods. The methods were validated by analysing and predicting the concentration of drugs in validation set which is different from the calibration set used for method development. The two methods were evaluated for predictive abilities by plotting the graph of predicted concentrations verses the actual known concentrations (Figure 4**)**. Figure 4 indicate the adequate concurrence between the actual concentration and predicted concentration of drugs. A different characteristic test was performed by plotting the graph of residuals concentration verses predicted concentration. In Figure 5, the residual values are randomly distributed near zero line indicating compatibility of methods. The values of correlation coefficient (r^2) and slope were

found to be good for both drugs in the validation set by CLS and ILS optimized methods and indicates that the both methods have good predictive abilities.

ASSAY OF MARKETED FORMULATION

Total twenty tablets of each brand were taken for assay. Tablets were accurately weighed and crushed to a powder. These tablet powder weighed accurately by taking the quantity equivalent to about 25 mg of EPL and 10 mg of TOR and transferred to 25 mL volumetric flask and dissolved in 10 mL of methanol. Then the sample solution was sonicated for 15-20 min and volume was adjusted with methanol and the solution was filtered by using a whatman filter paper no.42. Further dilutions were made to get the solution containing 25µg/mL of EPL and 10µg/mL of TOR. The assay was performed thrice for tablet formulation. The assay results for different brands are shown in Table 6. Summary of parameters for Classical Least Square and Inverse Least Square are depicted in Table 7.

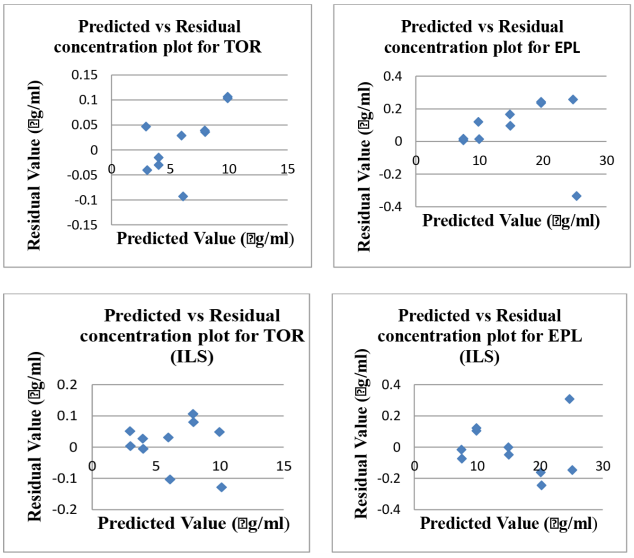

Figure 5: CLS – Expected vs. Residual Concentration of TOR and EPL, ILS – Expected vs. Residual Concentration of TOR and EPL.

CONCLUSION

Many drugs are used in combinations to improve the therapy of various ailments. The estimation of individual drugs from their combined dosage forms becomes a major challenge with respect time requirement for estimation and complexity of mixtures. The chemometric methods are cost effective compare to other methods and these methods are performed by using spectrophotometer and there is no need of prior separation of components. The developed chemometric assisted spectrophotometric methods are prompt and applicable for the simultaneous estimation of TOR and EPL from their mixed solutions and pharmaceutical

Table 6: Result of Assay for Torsemide and Eplerenone in marketed formulation by the CLS and ILS method.

For CLS method						
Formulation	Actual concentration mg/tablet		Amount obtained mg/tablet		% TOR ± S.D. (*n*=3)	% EPL ± S.D. (*n*=3)
	TOR	EPL	TOR	EPL		
PLANEP T 10	10	25	9.914	24.92	99.14 ± 0.1192	99.68 ± 0.1343
DYTORE E	10	25	9.96	25.06	99.66 ± 0.1393	100.27 ± 0.0637
EPNONE T	10	25	9.974	24.92	99.74 ± 0.1152	99.66 ± 0.2236
EPTUS T	10	25	10.05	25.08	100.52± 0.0772	100.34 ± 0.0890
EXENTA T	10	25	9.98	25.13	99.76± 0.14449	100.53 ± 0.2617
For ILS method						
Formulation	Actual concentration mg/tablet		Amount obtained mg/tablet		% TOR ± S.D. (*n*=3)	% EPL ± S.D. (*n*=3)
	TOR	EPL	TOR	EPL		
PLANEP T 10	10	25	9.97	25.06	99.76 ± 0.1156	100.24 ± 0.3439
DYTORE E	10	25	9.90	24.92	99.06± 0.0991	99.71 ± 0.7490
EPNONE T	10	25	10.03	25.02	100.34± 0.0466	100.08 ± 0.1892
EPTUS T	10	25	10.09	25.17	100.92± 0.1037	100.66 ± 0.1967
EXENTA T	10	25	9.91	25.05	99.10± 0.1236	100.20 ± 0.1414

Table 7: Summary of Parameters for CLS and ILS methods.						
Sr. No.	Parameters Torsemide		CLS		ILS	
			Eplerenone	Torsemide	Eplerenone	
1	Calibration design set		15			
2	Validation design set		10			
3	Spectral region		240-300 nm			
4	Linearity range (µg/mL)		3-10	7.5-25	3-10	7.5-25
5	RMSEP		0.06069	0.05097	0.05097	0.58312
6	% Recovery (Mean)		99.89	99.44	99.72	100.06
7	Assay	Planep T	9.914	24.92	9.97	25.06
		Dytore E	9.96	25.06	9.90	24.92
		Epnone T	9.974	24.92	10.03	25.02
		Eptus T	10.05	25.08	10.09	25.17
		Exenta T	9.98	25.13	9.91	25.05
8	LOD (µg/mL)		0.1822	0.1359	0.0630	0.0488
9	LOQ (µg/mL)		0.5523	0.4118	0.1909	0.1481

tablets dosage forms. The two chemometric methods; CLS and ILS were found to be accurate, precise, fast and economical for the multicomponent estimation. The proposed methods were validated according to ICH guideline and found suitable for estimation of the two drugs in quality control laboratories.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

ABBREVIATIONS

TOR: Torsemide; **EPL:** Eplerenone; **CLS:** Classical least square; **ILS:** Inverse least square; **µg:** microgram; **nm:** Nanometre; **HPLC:** High performance liquid chromatography; **HPTLC:** High performance thin layer chromatography; **LC-MS:** Liquid chromatography-Mass spectrometer.

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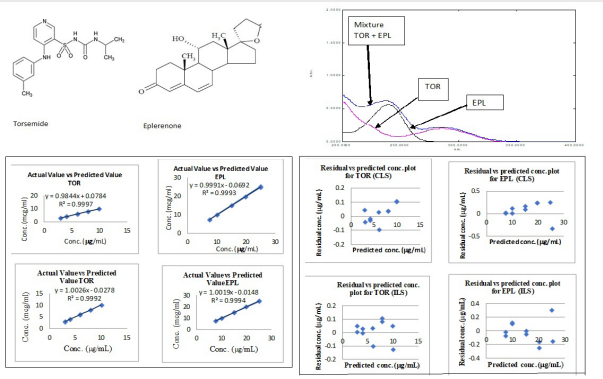
PICTORIAL ABSTRACT



SUMMARY

Chemometric approaches (Classical Least Square and Inverse Least Square) for the estimation of Torsemide and Eplerenone which are often employed for complicated matrix, have been developed and validated. The linearity covers the entire wavelength range as well as all possible concentrations. When all components are available in combination, it is commonly utilised for precise measurement of all constituents. The main aspect of chemometric methods is determining the coefficient value from the matrix, which may be done with the software MATLAB R2015a. The use of a low-cost instrument and a low-interference matrix are important for the successful use of both methods in routine analysis. For Torsemide and Eplerenone, different mixed solutions of concentration 3-10 µg/ml of Torsemide and 7.5-25 µg/ml of Eplerenone were measured between 240-300 nm. The lowest RMSEP values indicates application of method for quantitation of drugs.

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