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QUANTIFICATION OF LINEZOLID AND CEFUROXIME AXETIL BY CHEMOMETRICS ASSISTED AND RP-HPLC METHODS: DEVELOPMENT AND VALIDATION

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ABSTRACT: This paper describes simple, sensitive, accurate, rapid, precise and economical Chemometrics assisted and RP-HPLC methods for simultaneous estimation of Linezolid(LNZ) and Cefuroxime axetil(CEF) in bulk and tablet. Chemometrics offers a useful approach for an estimation of combined dosage form. The measurement carried out at wavelength 240 to 290nm with interval of 4nm for Linezolid and Cefuroxime axetil respectively. Chemometrics method were found to be linear ($R^2=0.999$) for all four methods CLS, ILS, PLS and PCR for LNZ and CEF respectively. HPLC method by using mobile phase Acetonitrile: water 65:35 with Thermo Synchronies C-18 (250mm x 4.6mm, 5 μ m) flow rate 0.8ml/min and detection wavelength 267nm. Retention time was found to be 3.573 min for LNZ and 4.273 min for CEF. HPLC method was found to be linear ($R^2=0.999$) for 6-30 μ g/ml for LNZ and 5-25 μ g/ml for CEF respectively. The applied methods Chemometrics and RP-HPLC were found to be successful for simultaneous estimation of LNZ and CEF in marketed dosage form.

INTRODUCTION: Linezolid(LNZ) is chemically (*S*)-*N*-({3-[3-fluoro-4-(morpholin-4-yl) phenyl] - 2-oxo-1,3-oxazolidin-5-yl}methyl)acetamide (**Fig. 1**). It is member of oxazolidinone class. It is used for the treatment of serious infection caused by Gram positive bacteria that resistance to other antibiotics. The main uses are infections of the skin and pneumonia although it may be use for a variety of other infections.

Oxazolidinone bind to the 50S subunit of the prokaryotic ribosome, preventing it from complexing with the 30S subunit, mRNA, initiation factors and formylmethionyl-tRNA. The net result is to block assembly of a functional initiation complex for protein synthesis, thereby preventing translation of the mRNA. Cefuroxime axetil (CFA) is a second-generation cephalosporin that contains the classic β -lactam ring structure. Cefuroxime axetil is an ester prodrug of cefuroxime, which is rendered more lipophilic by esterification of carboxyl group of the molecule by the racemic 1-acetoxyethyl bromide, thus enhancing absorption. The absorbed ester is hydrolysed in the intestinal mucosa and in portal circulation. Products of hydrolysis are active cefuroxime, acetaldehyde and acetic acid. Cefuroxime is chemically (1*R*,3*S*)-1-

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[(acetyl) oxy] ethyl- (6R, 7R)-3-(carbamoyloxy) methyl]-7-[(Z-2-furan- 2yl)-2-(methoxy imino) acetyl) amino]-8-oxo-5-thia-1- aza bicyclo- (4,2,0)-oct-2-ene-2-carboxylate. (**Fig.1**) It is used as an antibiotic for the treatment of many type of bacterial infections such as bronchitis, sinusitis, tonsillitis, ear infections, skin-infections, urinary tract infections.

The literature survey revealed that there are several analytical methods reported for LNZ either individually like spectrophotometric method ¹⁻³, RP-HPLC ⁴ or in combination with other drugs. ⁵ For CEF spectrophotometric method ⁶⁻¹¹, RP-HPLC method ^{12, 13}, several analytical methods reported for simultaneous determination of these drug with other drug in pharmaceutical formulation. ^{14, 15} also reported HPTLC method. ¹⁶ Present work describes simple, rapid, accurate and precise Chemometrics assisted method and RP-HPLC. For simultaneous estimation of LNZ and CEF was validated as per ICH guideline. ¹⁷

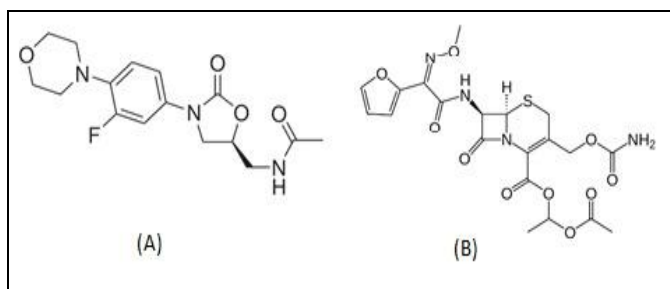


FIG. 1: CHEMICAL STRUCTURE OF (A) LNZ AND (B) CEF

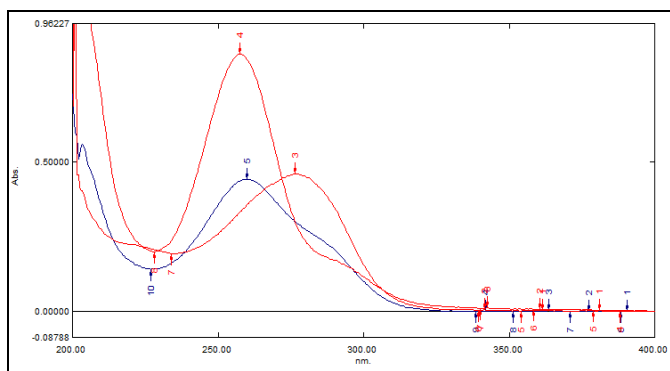


FIG.2: UV SPECTRA OF (3) CEF, (4) LNZ AND (5) MIXTURE

MATERIAL AND METHODS:

Apparatus and Software:

Shimadzu UV-1700 double beam spectrophotometer_ Data acquisition and manipulation was performed using UV Probe 2.10 software.

Chemometrics is done by Design expert 7.0, Matlab r2009a, Unscramble x 10.3 and Microsoft office.

HPLC was performed on isocratic Shimadzu (Shimadzu Corporation, Kyoto, Japan) chromatographic system equipped with Shimadzu LC-20AT pump and Shimadzu SPD-20AV absorbance detector Data acquisition and integration was performed using Spinchrome software (Spincho biotech, Vadodara).

Reagents and materials:

Linezolid and Cefuroxime axetilsamples were obtained from Cadila healthcare, Ahmedabad and Vapi care Pvt Ltd. Vapi respectively. LINOX XT Tablet (Unichem) was purchase from local market. Methanol AR grade (rankem). Acetonitrile HPLC grade (Fischer). Double distilled water (filtered by 0.2µm membrane filter paper by vacuum filtration).

Preparation of standard stock solution:

An accurately weighed standard LNZ and CEF powder (25 mg) were weighed and transferred to 25 ml separate volumetric flasks and dissolved in methanol. The flasks were shaken and volumes were made up to mark with methanol to give a solution containing 1000 µg/ml (first stock) of each LNZ and CEF.

Withdraw 2.5 ml solution form first stock then make up to 25 ml with methanol to give a solution containing 100 µg/ml(second stock) of each LNZ and CEF.

A) Chemometrics assisted methods for simultaneous estimation of linezolid & cefuroxime axetil: ^{18, 19}

- Chemometrics methods are one kind of multivariate analysis i.e. considering more than one variable at a time.
- Here, we are considering absorbance at 13 different wavelengths (240 to 290nm with interval of 4.0nm) – 13 variables in contrast to other univariate methods where absorbance at only one wavelength is considered (Absorbance matrix ‘A’)

Four different methods:

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

Preparation of Calibration Set mixture:

Total twenty-three binary mixture standards with required concentrations (as shown in **Table 1**) were prepared from stock solutions.

Preparation of Validation Set mixture:

Total thirteen binary mixture standards with required concentrations (as shown in **Table 1**) were prepared from stock solutions.

Producing Absorbance Matrix A:

Absorbance matrix A was produced by measuring absorbance at 13 wavelengths in the spectrum region between the 240nm to 290 nm at 4nm wavelength interval. This region was selected because it contained most relevant information about both the drugs. The spectra of prepared binary mixture standards were recorded in the range of 240 to 290nm. Absorbance values in this wavelength region with interval of 4nm were recorded.

TABLE 1: CALIBRATION SET AND VALIDATION SET

Calibration set		Validation set	
LNZ	CEF	LNZ	CEF
9	15	12	15
9	10	6	2.5
18	2.5	18	12.5
9	5	12	5
9	12.5	15	7.5
3	15	6	15
3	5	9	7.5
18	7.5	3	10
3	7.5	18	5
3	12.5	18	10
6	5	6	12.5
15	2.5	3	2.5
12	2.5	15	5
6	7.5		
15	10		
18	15		
6	10		
15	12.5		
12	12.5		
12	10		
15	15		
9	2.5		
12	7.5		

1. Classical Least Squares(CLS):

The CLS method assumes the Beer's law model with the absorbance at each wavelength being proportional to the component concentrations. In matrix notation, the Beer's law model for m calibration standards containing l chemical components with spectra of n digitized absorbance is given by

$$A = C * K$$

Where, A is the m x n matrix of calibration spectra, C is the m x l matrix of component concentrations, K is the l x n matrix of Absorptivity which represents the matrix of pure component spectra at unit concentration and unit path length. Thus, the spectral matrix A is represented as the product of two smaller matrices C and K.(Figure:3) The pure component spectra (rows of K) are the factor loadings (also called loading vectors) and the chemical concentrations (columns in C) are the factors (or scores). In simplified manner, it can be

said that each component will be having specific Absorptivity at each particular wavelength being considered. Each row of K matrix represents spectrum of one pure component at its unit concentration. K matrix will have as many rows as components and as many columns as wavelengths. Once we have matrices A and C, we can determine K by following equation:

$$K = \text{pinv}(C) * A$$

Where, $\text{pinv}(C)$ is the pseudo inverse of concentration matrix C.

For predicting the unknown concentration of a mixture from its absorbance matrix, following equation is used:

$$C = A * \text{pinv}(K)$$

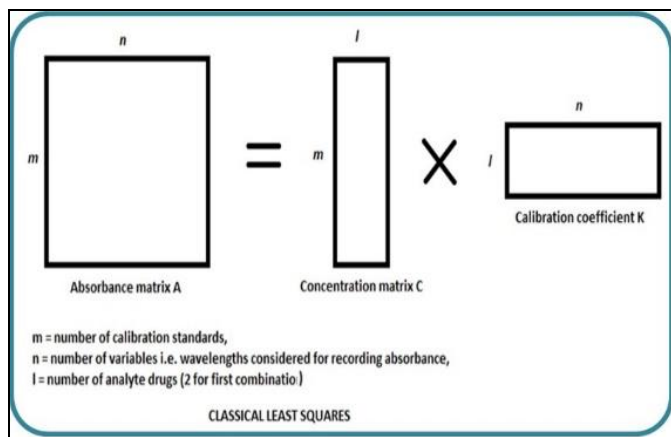


FIG. 3: CLS PROCEDURE

Inverse Least Squares(ILS):

The inverse least squares method assumes that concentration is a function of absorbance. The inverse Beer’s law model for m calibration standards with spectra of n digitized absorbances is given by

$$C = A * P$$

Where, C and A are as before, P is the n x l matrix of the unknown calibration coefficients relating the l concentrations to the spectral intensities. The inverse representation of Beer’s law has the significant advantage that the analysis based on this model is invariant with respect to the number of chemical components, l, included in the analysis. Unlike CLS, ILS does not require that we provide concentration values for all of the components

present. Instead the model allows us to pick up only that portion of spectral absorbance that correlates well to the concentration. Once we have matrices A and C, we can determine P by following equation:
 $P = \text{pinv}(A) * C$

Pseudo inverse of matrix A is calculated instead of inverse as explained in Classical Least Squares method. (We can calculate P for as many components as we provide in matrix C i.e. if all the components in matrix C are not known, P will be calculated only for those components which are known and present in matrix C). For predicting the unknown concentration of a mixture from its absorbance matrix, (Fig.4) following equation is used:

$$C = A * P$$

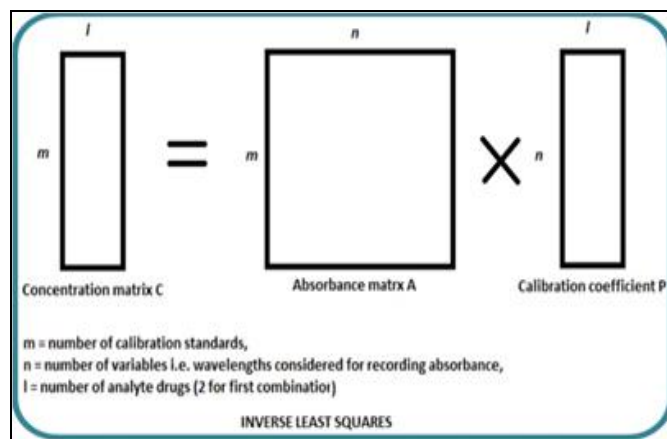


FIG. 4: ILS PROCEDURE

Principal Component Regression(PCR):

PCR is a method by which the dimensionality or complexity of the data is reduced. With reference to application for spectrophotometric analysis, absorbance matrix concerns to a large pool of data containing n variables (wavelengths, one column for each) and m samples (calibration standards, one row for each). Each sample can be presented as a point in n dimensional space according to its absorbance values at different wavelengths. Thus, one sample is described by n variables. PCR is a tool which reduces number of variables to only a few components, referred to as principal components (PCs). They are computed in such a way that the first PC is the one that carries most information (or in statistical terms: most explained variance). The second PC will then carry the maximum share of the residual information (i.e. not taken into account by the previous PC) and so on.

All the PCs will be orthogonal to each other and they are ranked in a manner so that first PC will explain maximum variance in the data. Theoretically, there can be as many PCs as the number of actual variables (n). But only first few PCs are considered because they explain almost all the variance in the data.

After reducing the dimensionality of data to a few PCs, next step is regression to relate these PCs with concentration. There will be individual regression for each drug present in the sample. Thus, PCR deals with only one response variable (concentration) at a time. PCR Procedure shown in **Fig.5**.

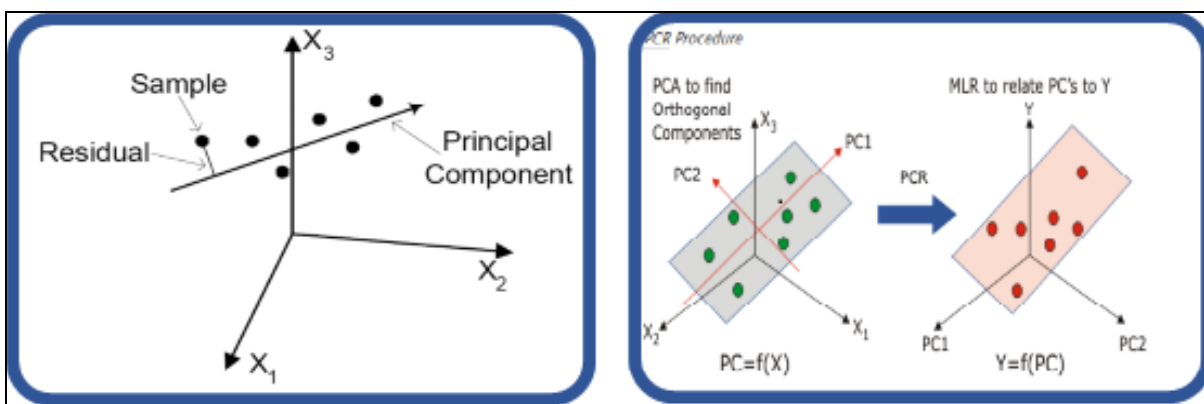


FIG. 5: PCR PROCEDURE

Partial Least Squares(PLS):

PLS models both the X- and Y-matrices simultaneously to find the latent variables in X that will best predict the latent variables in Y. This method is called projection to latent structures. These PLS latent variables are similar to principal components, and will be referred to as PCs or factors. PLS procedure is shown in **Fig. 6**. In PCR, we find PCs for only X matrices (variables) and then these PCs are related directly to Y (sample concentration). Here in PLS, PCs are computed for

X and Y both. And then PC of X is related with PC of Y. PLS can handle multiple responses in Y at a time in contrast to PCR. The difference between PCR and PLS lies in the algorithm. PLS use the information lying in both X and Y in order to fit the model. It switches between X and Y iteratively to find the relevant PCs. So PLS often needs fewer PCs to reach the optimal solution because the focus is on the prediction of the Y-variables (not on achieving the best projection of X as in PCR).

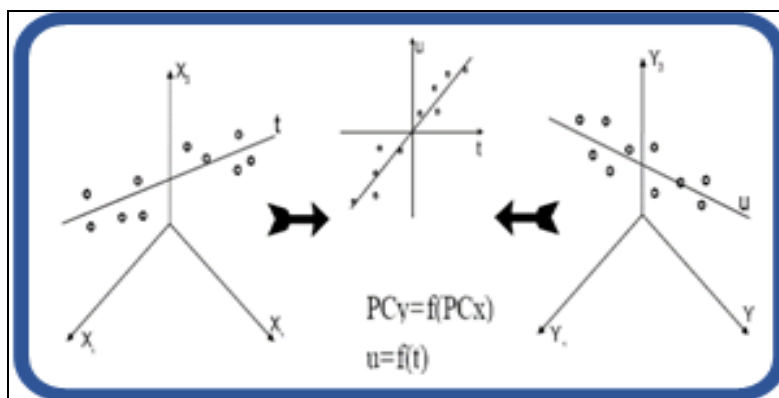


FIG.6: PLS PROCEDURE

Validation of ILS, CLS, PCR and PLS Methods: 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 0 intercept. The predicted vs. actual concentration plots of prepared validation samples are shown in **Fig.7 and 8**. It was

noticed that LNZ and CEF in all samples lay on straight line & the equation of this line are shown on the graph. This indicates that the predicted

ability of the validation set is very much better in terms of recovery.

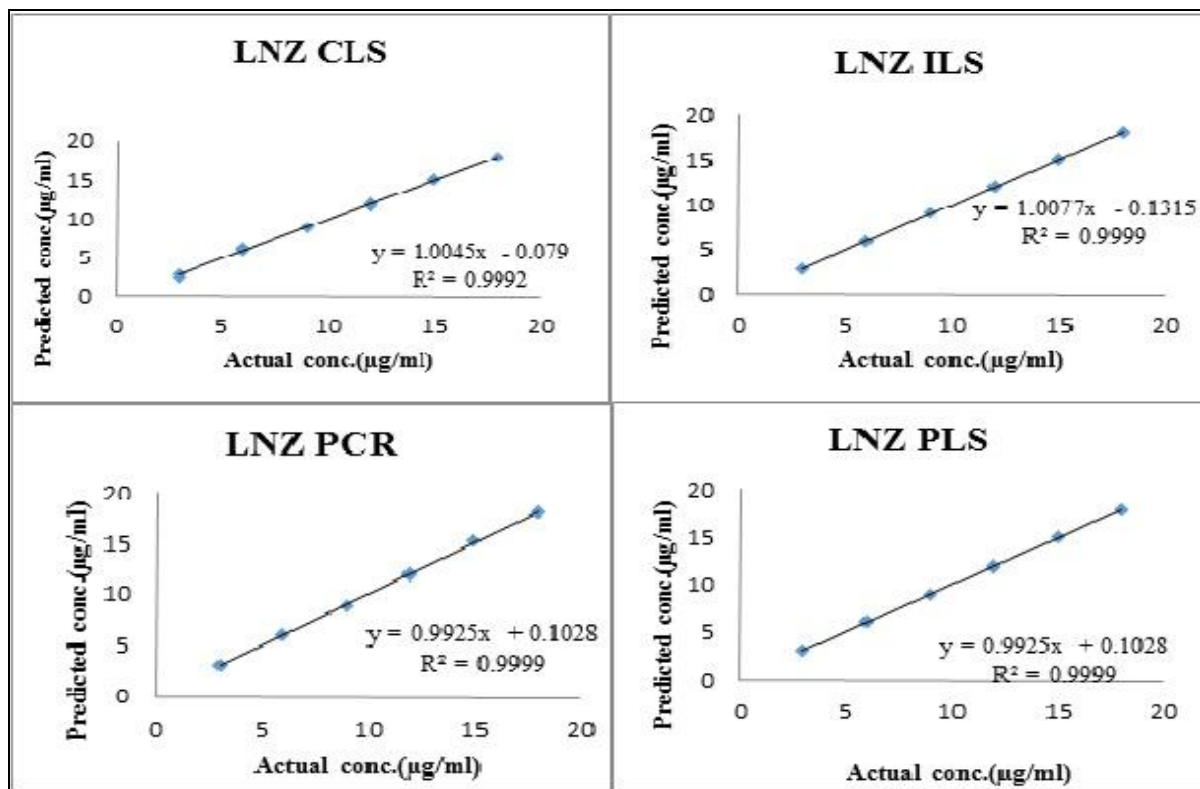


FIG.7: PREDICTED Vs ACTUAL CONCENTRATION GRAPHS FOR LNZ

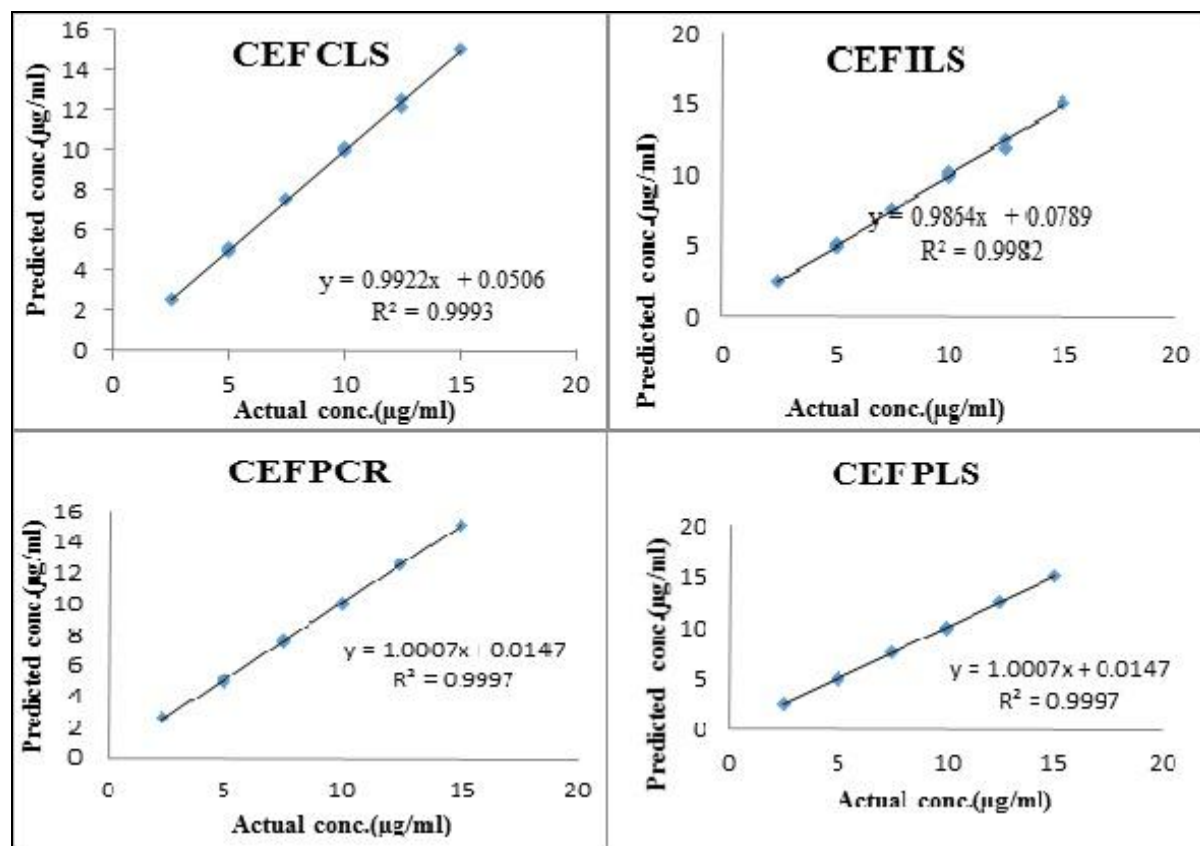


FIG. 8: PREDICTED Vs ACTUAL CONCENTRATION GRAPHS FOR CEF

Residual vs Actual concentration:

Plot the differences between actual & predicted concentration (Residuals) were plotted against actual concentration of validation samples. This tool is used to determine whether the model accounts for the concentration variation in the validation set and it also provides information

about how well the method will predict the future sample. For the validation set it can be found that the residual values more close to zero & more randomly distributed. **Fig. 9** and **10** shows concentration residual vs. actual concentration plot for all methods.

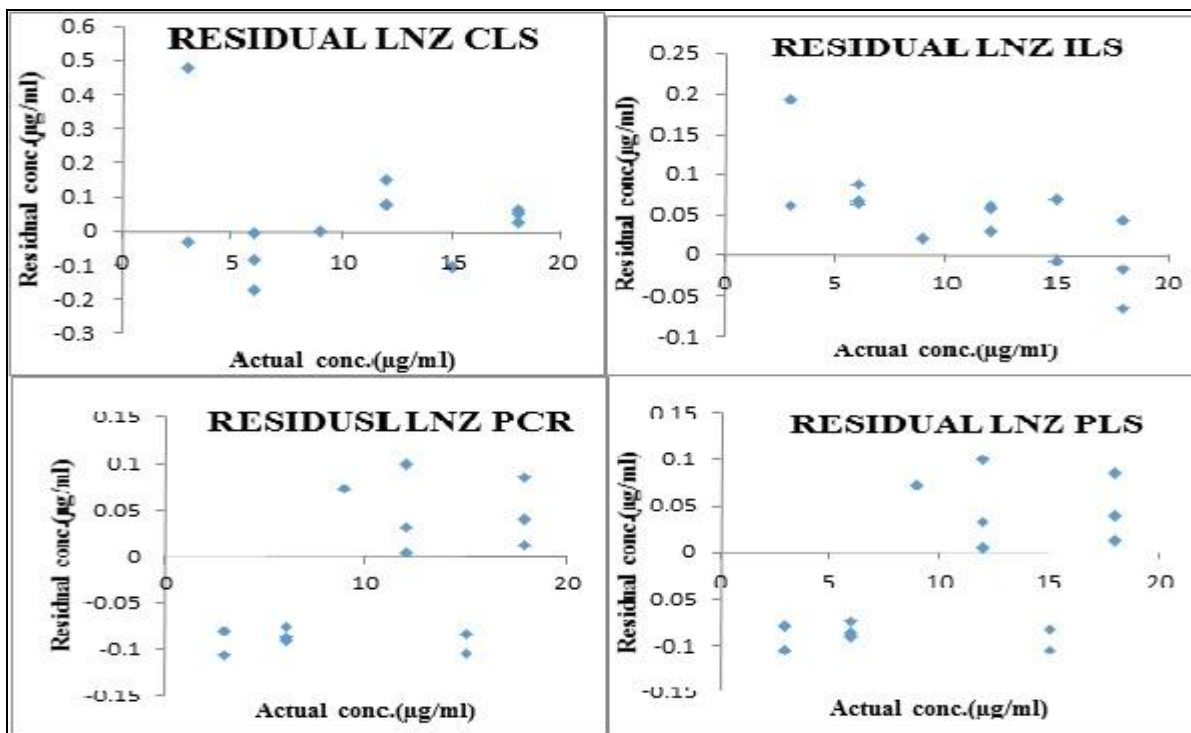


FIG.9: RESIDUAL Vs ACTUAL CONCENTRATION GRAPH OF LNZ

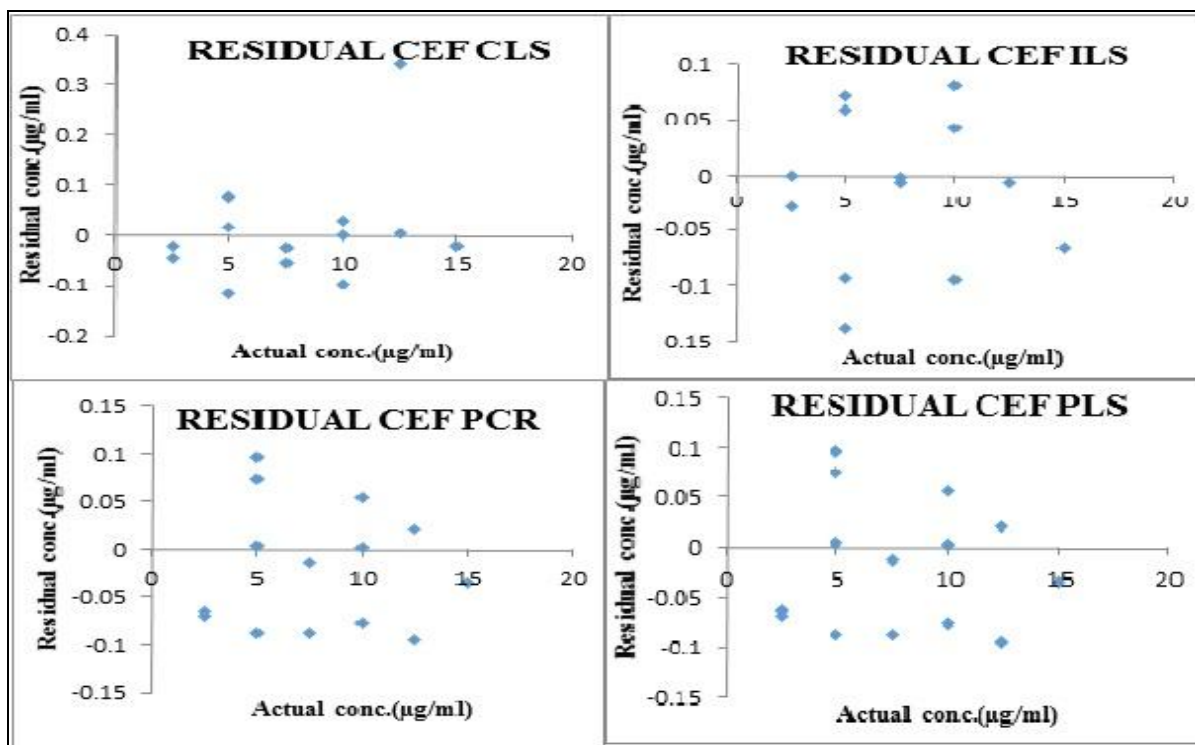


FIG. 10: RESIDUAL VS ACTUAL CONCENTRATION GRAPHS OF CLS

Applicability to formulation:

Sample solution was scan at 240 to 290nm with interval of 4nm. From the absorbance amount of drug were computed. Result were shown in **Table 2**

TABLE 2: APPLICABILITY TO FORMULATION (n=6)

Method	LNZ	CEF
CLS	98.658 ± 0.317	102.47 ± 0.619
ILS	99.47 ± 0.264	100.13 ± 0.416
PCR	98.764 ± 0.298	102.614 ± 0.773
PLS	100.16 ± 0.149	101.503 ± 0.572

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 concentration. It is calculated from following formula.

$$RMSEP = \sqrt{\frac{\sum_{I=1}^N (C_{Actual} - C_{Predicted})^2}{N}}$$

Where, N is the number of samples used for validation i.e. 14. The results of future predictions can then be presented as “predicted values ±2•RMSEP”. RMSEP for LNZ and CEF by Chemometrics Methods are shown in **Table 3**.

TABLE 3: RMSEP FOR LNZ AND CEF

Drug	RMSEP			
	CLS	ILS	PCS	PCR
LNZ	0.1536	0.0741	0.0770	0.0770
CEF	0.1066	0.1673	0.0646	0.0646

B) RP-HPLC method:**Chromatographic condition:**

Column: Thermo Synchronis C-18 (250mm x 4.6mm, 5µm)

Mobile phase: acetonitrile: water in 65:35(v/v)

Flow rate: 0.8ml/min

Detection wavelength: 267nm

Column temperature: ambient

Preparation of standard stock solution:

An accurately weighed standard LNZ and CEF powder (25 mg) were weighed and transferred to

25 ml separate volumetric flasks and dissolved in ACN. The flasks were shaken and volumes were made up to mark with ACN to give a solution containing 1000 µg/ml (first stock) of each LNZ and CEF.

Withdraw 2.5 ml solution form first stock then make up to 25 ml with mobile phase to give a solution containing 100µg/ml (second stock) of each LNZ and CEF.

Preparation of mixed standard solution:

From the above second stock solution accurately withdraw 0.6, 1.2, 1.8, 2.4, 3.0ml (6, 12, 18, 24, 30µg/ml) LNZ and 0.5, 1.0, 1.5, 2.0, 2.5ml (5, 10, 15, 20, 25µg/ml) CEF then made up to 10ml with mobile phase.

Preparation of sample solution:

Twenty tablets were weighed and finely powdered. An accurately weighed portion of the powder equivalent to 600mg of LNZ and 500mg of CEF was transferred to 100ml volumetric flask and sufficient methanol was added and sonicated for 10 min. The solution was filtered through Whatmann filter paper (No. 42) into 100ml volumetric flask and then diluted up to volume with methanol to get stock 1 solution. Withdraw 1ml from above prepared solution and diluted up to 100mL with methanol to get the stock 2 solution. Different volumes of these solutions were taken and diluted with methanol to get different concentrations of LNZ and CEF. The solutions prepared in this manner were then subjected to analysis by developed method. The procedure was repeated for six times to get reproducible results.

Method validation:

The proposed method was validated according to the International Conference on Harmonization (ICH) guidelines.

1) Linearity:

Linearity was performed by taking from stock solution aliquots 0.6, 1.2, 1.8, 2.4, 3.50ml (6, 12, 18, 24, 30µg/ml) LNZ and 0.5, 1.0, 1.5, 2.0, 2.5ml (5, 10, 15, 20, 25µg/ml) CEF then make up to 10ml with mobile phase. Volume of 20µl was injected five times for each concentration level and calibration

curve was constructed by plotting a peak area versus drug concentration. (Fig. 11,12 and Table 4)

TABLE 4: CALIBRATION RANGE

LNZ		CEF	
Concentration(µg/ml)	Area	Concentration(µg/ml)	Area
6	197.542	5	141.366
12	378.363	10	276.167
18	556.957	15	411.717
24	729.815	20	531.004
30	924.760	25	664.946

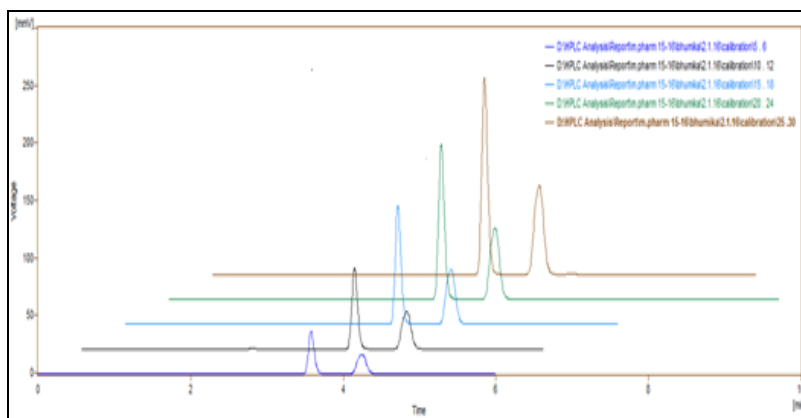


FIG.11: OVERLAIN CHROMATOGRAM

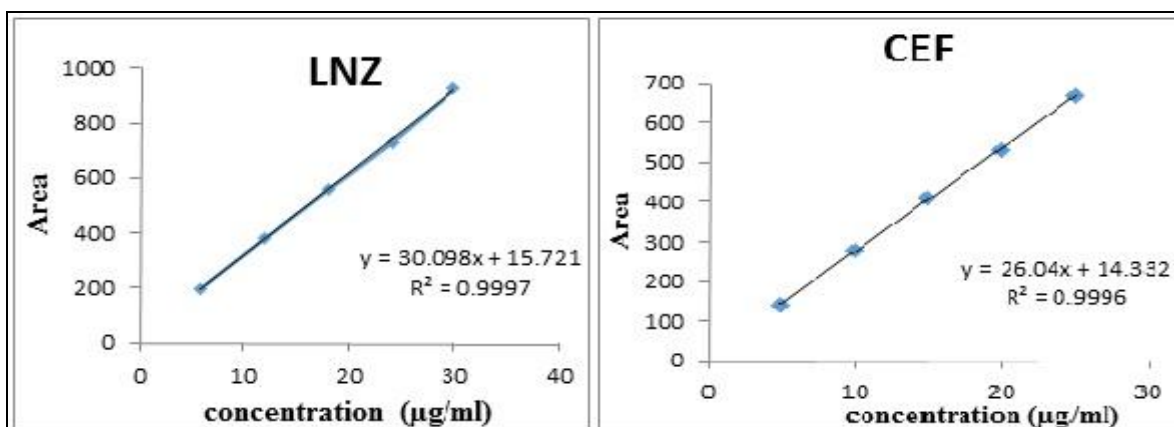


FIG. 12: CALIBRATION CURVE OF LNZ (a) AND CEF (b)

Accuracy:

It was done by recovery study. Sample solution were prepared by spiking at about 80%, 100%, 120%.

Precision:

Three sample were prepared and analysed as per the test method on same day and different days and calculated the %RSD.

Limit of detection and Limit of quantification:

The parameter LOD and LOQ were determined on the basis of response and slope of the regression. All results of parameter shown in Table 5.

TABLE 5: SUMMARY OF VALIDATION PARAMETER

	LNZ	CEF
Analytical wavelength(nm)	267nm	
Linearity range(µg/ml)	6-30	5-25
Retention time(min)	3.573	4.273
Regration equation	Y=30.098x+15.721	Y=26.04+14.332
Correlation coefficient	0.9997	0.9996
Intraday precision(%RSD)	0.93469	0.94615
Intreday precision(%RSD)	1.556	1.236
LOD	0.06287	0.55625
LOQ	0.19038	1.6856
Accuracy (mean% recovery)	100-101.3%	98-101.5%

Robustness:

Robustness was performed by deliberately changing the chromatographic conditions. The flow rate of the mobile phase was changed from 0.8 ± 1

mL/min. The organic strength was varied by ± 2 ml. The wavelength was varied by ± 4 . Standard solution was injected six times in replicate for each change. Results were shown in **Table 6**.

TABLE 6: ROBUSTNESS

Factor	Retention time (min)		Peak Area (mV.s)	
	LNZ	CEF	LNZ	CEF
A.: Wavelength				
263 nm	3.557	4.263	377.945	276.167
267 nm	3.575	4.273	378.363	277.675
271 nm	3.581	4.289	379.124	278.154
Mean \pm SD	3.571 \pm 0.0124	4.275 \pm 0.0131	378.743 \pm 0.5381	277.914 \pm 0.336
B. : Flow rate				
0.7	2.982	3.967	377.379	276.245
0.8	3.569	4.281	378.569	277.548
0.9	3.798	4.325	379.233	278.145
Mean \pm SD	3.449 \pm 0.1952	4.191 \pm 0.1952	378.373 \pm 0.1771	277.312 \pm 0.9716
C.: Organic ratio				
63:37	3.567	4.284	377.978	277.842
65:35	3.579	4.325	378.125	278.271
67:33	3.589	4.401	377.379	279.383
Mean \pm SD	3.34 \pm 0.439	4.336 \pm 0.0593	378.494 \pm 0.395	278.488 \pm 0.8078

Applicability of sample:

Sample and standard solution was injected separately into HPLC system. From the peak area

amount of drug were computed. Result were shown in **Table 7**.

TABLE 7: APPLICABILITY OF SAMPLE

Marketed formulation (LINOX -XT)			
Labelled claim: LNZ CEF =600mg, 500mg			
Sr no.	Method	LNZ \pm SD	CEF \pm SD
1.	RP HPLC	100.728 \pm 0.348	99.501 \pm 0.619

System suitability test parameter shown in **Table 8**.

TABLE 8: SYSTEM SUITABILITY TEST

PARAMETER	DATA OBTAINED (n=6)	
	Linezolid	Cefuroxime Axetil
Retention time (min) \pm SD	3.15 \pm 0.0513	4.27 \pm 0.0239
Theoretical plate \pm SD	9365 \pm 315.56	5170 \pm 245.93
Tailing factor \pm SD	1.28 \pm 0.0963	1.029 \pm 0.0158
Resolution \pm SD	3.62 \pm 0.296	

RESULT AND DISCUSSION: Applicability of Chemometrics assisted and RP-HPLC methods are an effective tool for simultaneous estimation of LNZ and CEF which offers striking advantage in terms of time required for analysis, simplicity, accuracy, and precision. All the methods are found to be applicable for marketed formulation. The methods were validated and satisfactory results were produced.

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CONFLICT OF INTREST: There is no conflict of interest.

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