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QBD approach to develop stability indicating RP-HPLC method development for Levosulpiride and Ilaprazole

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***Abstract*---**Objectives: As per requisition of current regulatory requirements, simple, rapid and sensitive method by 3^3 factorial QbD approach was established and validated for Levosulpiride and

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Ilaprazole by RP-HPLC. Method: A simple RP-HPLC method has been developed and validated with different parameters such as linearity, precision, repeatability, LOD, LOQ, accuracy as per ICH guidelines (Q^2R^1). Statistical data analysis was done for data obtained from different aliquots Runs on Agilent Tech. Gradient System with Auto injector, UV (DAD) & Gradient Detector. Results: Equipped with Reverse Phase (Agilent) C_{18} column (4.6mm x 250mm; 5µm), a 20µl injection loop and UV730D Absorbance detector at 219 nm wave length and running chemstation 10.1 software and drugs along with degradants were separated via Methanol: (0.1% OPA) Water (45:55) of pH 3.2 as mobile phase setting flow rate 0.6 ml/min at ambient temperature, retention time at 4.257 min and 5.547 min. with good peak shape (Theoretical plates of 6972 of Levosulpiride and 3521 of Ilaprazole). The LOD and LOQ of Levosulpiride were found to be 1.8208µg/ml and 5.5176µg/ml. The LOD and LOQ of Ilaprazole were found to be 0.3676µg/ml and 1.1139 µg/ml analytical method that concluded. Conclusion: There are no interfering peaks underperformed degradation conditions. Therefore, a sensitive, robust, accurate and stability indicating method was developed with high degree of practical utility.

***Keywords*---**Levosulpiride, Ilaprazole, QbD, RP-HPLC, Stability Study, method development, validation.

Introduction

The concept of "Quality by Design" (QbD) was defined as an approach which covers a better scientific understanding of critical process and product qualities, designing controls and tests based on the scientific limits of understanding during the development phase and using the knowledge obtained during the life-cycle of the product to work on a constant improvement environment (Raman, N. 2015). QbD describes a pharmaceutical development approach referring to formulation design and development and manufacturing processes to maintain the prescribed product quality (Patel, M. N., 2016). Guidelines and mathematical models are used to ensure the establishment and use of the knowledge on the subject in an independent and integrated way. Drugs play a vital role in the progress of human civilization by curing diseases. Analytical chemistry is divided in two branches qualitative and quantitative (Tol, T., 2016).

Levosulpride (LEVO) is a prokinetic, N-[[(2S)-1-Ethylpyrrolidin-2-yl] methyl] -2-methoxy -5- sulfamoylbenzamide (Fig. 1). LSP is an atypical antipsychotic and a prokinetic agent. It is used in several indications like depression, psychosis, somatoform disorders, emesis and dyspepsia (Silambarasan, S. P., 2010). Ilaprazole (ILA) is a proton pump inhibitor, chemically 2-[(RS)-[(4-methoxy-3-methylpyridin-2-yl)methyl]sulfinyl]-5-(1H-pyrrol-1-yl)-1Hbenzimidazole (Fig. 2) is a new proton pump inhibitor used in the treatment of peptic ulcer disease, dyspepsia, gastro esophageal reflux disease and duodenal ulcer which reduces acid secretion by inhibiting the parietal cell H+/K+ ATP pump (Khimani, R., 2018).

Levosulpiride and Ilaprazole are available in combination in capsule dosage form that have been used for the treatment of gastroesophageal reflux syndrome (GERD) and in treatment of psychic patient and to suppress acid secretion in stressed condition (Rami, D. H., 2018).

Literature survey revealed that UV, HPLC and HPTLC methods are reported for the estimation of Ilaprazole and levosulpiride either in alone or in combination with other drugs. However no method has been reported for simultaneous estimation of these drugs in combination using QbD based 3^3 factorial designing. (Sharma B.K., 1981 and Sharma B.K. 2005). The present work is an attempt to quality by design (QbD) approach to develop stability indicating RP-HPLC method development for levosulpiride and ilaprazole.

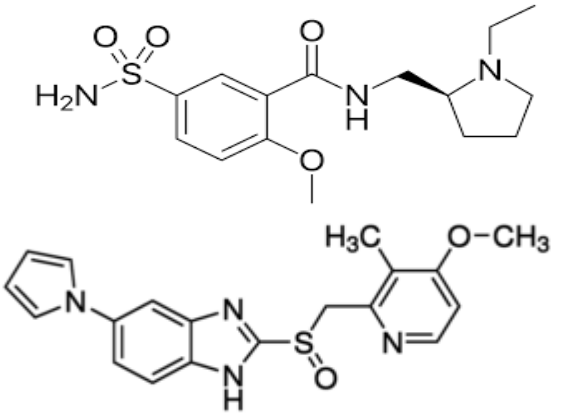


Fig. 1: structure of Levosulpiride and Ilaprazole

Chemicals and Reagents

Reference standards of Levosulpiride and Ilaprazole was obtained as gift sample from Swapnroop drug and pharmaceutical, Aurangabad, Maharashtra, India. Pharmaceutical formulation was purchased from local market (Brand: Blokcid L tablet labelled claim Levosulpiride 75 and Ilaprazole 10 mg make Ipca laboratories Ltd). The HPLC grade solvents used were of E-Merck (India) Ltd., Mumbai. HPLC grade Acetonitrile, Methanol and Ortho Phosphoric Acid (Merck, Mumbai, India) were used in the analysis. HPLC grade water was prepared using Millipore purification system (Kaur, N. 2021).

Instruments

The analysis of the drug was carried out on Agilent Tech. Gradient System with Auto injector, UV (DAD) & Gradient Detector. Equipped with Reverse Phase (Agilent) C_{18} column (250mm×4.6mm×5µm), a 20µl injection loop and UV730D Absorbance detector and running chemstation 10.1 software.

RP-HPLC Optimised Chromatographic Condition using QbD

Column C_{18} (250mm×4.6mm), particle size packing 5µm; detection wavelength 219 nm; flow rate 0.6 ml/min; temperature 26^0C ambient; sample size 20 µl;

mobile phase methanol: water (OPA 0.1% PH 3.2) (45:55); run time 15 min. The retention time for Levosulpiride and Ilaprazole were found at 2.9333 min and 6.9667 min respectively Fig. 2. (Tamboli, R., 2014).

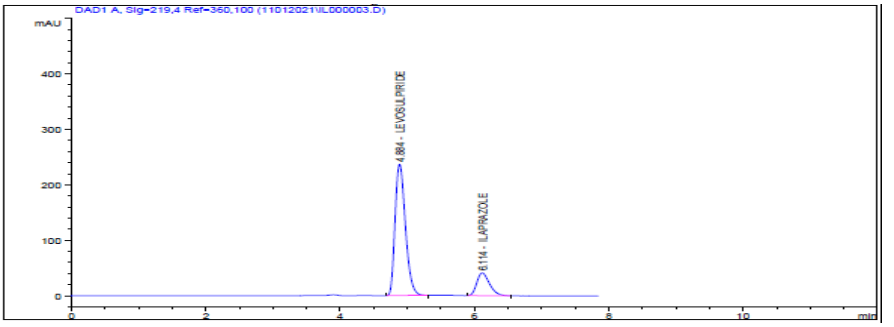


Fig. 2: chromatogram of standard LEVO and ILA at 219 nm

Preparation of standard solution

All solutions were prepared on a weight basis and solution concentrations were also measured on weight basis to avoid the use of an internal standard Pharmaceutical formulation which is available in the market in the proportion of 2:15 (Shetty, P. R., 2014).

Stock preparations

Standard stock solution was prepared by dissolving 15 mg LEVO and 2 mg ILA in 10 ml clean dry volumetric flask and dilution was upto the mark with Methanol to obtain final concentration of LEVO (1500 µg/ml) and ILA (200 µg/ml). All the stock solutions were filtered through 0.45 µm membrane filter (Shelke, P. G., 2015).

Detection of λ_{max} : The sample solution has been prepared and scanned in the UV region of 200-400 nm and the spectrum showed the maximum a bsorbance at 219 nm Fig. 3.

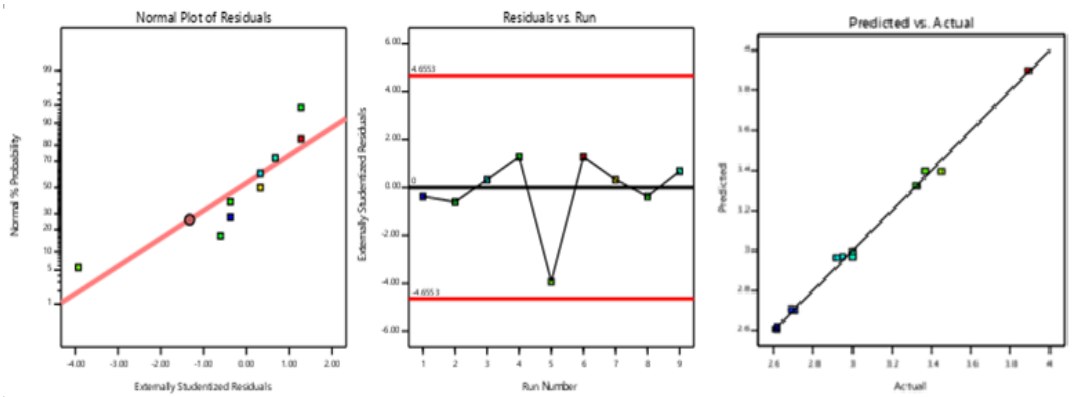


Fig. 3A: Normal Plot of Residuals for retention time for Predicted Vs Actual data ranging from 1.9 to 3.2

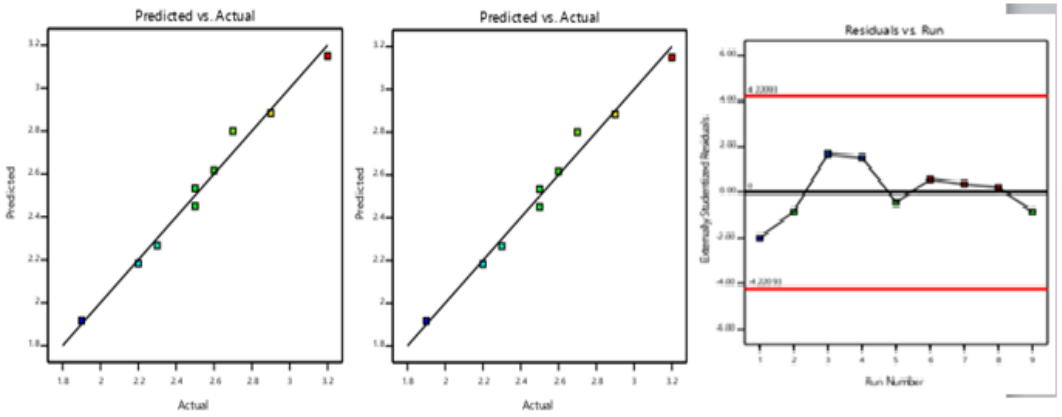


Fig. 3B: Normal Plot of Residuals for Retention Time and Plot of Predicted Vs Actual Data for Retention Time by the value of 3222.92 to 4285.84

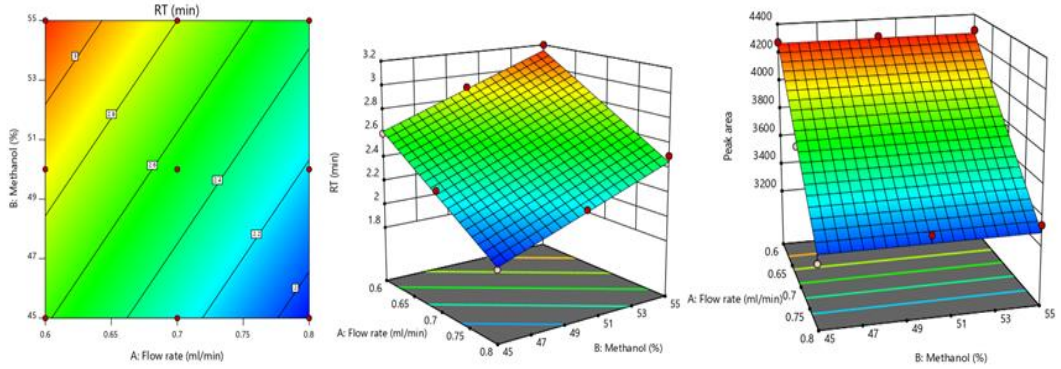


Fig. 3C: Contour Plot of residuals for % of Methanol, Flow rate and Peak Area by the value of 3222.92 to 4285.84

QbD approach to analysis

The application of QbD in HPLC method development commences with establishing analytical objectives based on sound science to ensure consistent method performance characteristics are achieved. The use of QbD for an analytical method commences with defining the target analytical profile in which the pre-defined objectives for method performance must be appropriately validated and documented.

Thus the objective of this work was to perform experimental design by using Design Expert Software leading to develop simple, rapid and sensitive method by QbD approach and validated as per ICH Guidelines (Q2R1) for Levosulpiride and Ilaprazole and its stability indicating method by RP-HPLC. Further statistical data analysis to be done along with numerical and graphical optimization to develop Analytical Design Space (ADS).

Method Validation

Calibration Curve

A calibration curve was constructed succeeding replicate (n=6) analysis of five standards of 75, 150, 225, 300, 375 µg/ml of Levosulpiride and 10, 20, 30, 40, 50 µg/ml of Ilaprazole. The peak height ratio of drugs was calculated and plotted AUC versus concentration after which least squares linear regression analysis of data was undertaken to establish the equation for the best fit line and the correlation coefficient (R^2) to authorise linearity. Samples were injected and peaks were recorded at 219 nm and the graph plotted as concentration of drug verses peak area as shown in Table 1 -2.

Table 1: Linearity data for Levosulpiride

Conc. µg/ml	Peak area(µV.sec)		Average peak area (µV.sec)	S.D. of Peak Area	% RSD of Peak Area
	1	2			
75	2541.55	2536.26	2538.90	3.74	0.15
150	5201.41	5198.16	5199.79	2.30	0.04
225	7574.47	7596.96	7585.71	15.90	0.21
300	10047.50	10000.80	10024.15	33.02	0.33
375	12524.70	12576.20	12550.45	36.42	0.29
Equation		y = 33.13x-125.5			
R^2		0.999			

Table 2: Linearity data for Ilaprazole

Conc. µg/ml	Peak area(µV.sec)		Average peak area (µV.sec)	S.D. of Peak Area	% RSD of Peak Area
	1	2			
10	533.84	534.30	534.07	0.32	0.06
20	1105.93	1109.39	1107.66	2.44	0.22
30	1684.35	1691.05	1687.70	4.74	0.28
40	2182.37	2164.98	2173.68	12.30	0.57
50	2709.46	2724.21	2716.84	10.43	0.38
Equation		y = 14.31x + 14.52			
R^2		0.999			

Precision

Intra-day (repeatability) precision was established following analysis of replicate samples (n=6) at three concentrations indicative of low, medium and high levels within the linear range *viz.*, 150, 225 and 300 µg/ml of LEVO and 20, 30 and 40 µg/ml of ILA. Analysis was performed over a short period of time on the same day. Inter-day precision or reproducibility was assessed at low, medium and high concentration on three consecutive days and the percent relative standard deviation (% RSD) was used to assess intra- and inter-day precision. An upper limit of 2% was used to confirm precision in our laboratory. Precision of an analytical method is usually expressed as standard deviation or relative standard

deviation. Table 3 and 4 describes the Intraday, Interday and Repeatability of method.

Table 3: Results of precision studies (intra-day and inter-day)

Drug	Concⁿ (µg/ml)	Intraday Precision		Interday Precision	
		Mean± SD	%Amt Found	Mean± SD	%Amt Found
LEVO	150	5195.4± 1.07	102.02	5195.43± 4.09	102.02
	225	7558.9±12.81	99.72	7568.10±2.19	99.84
	300	10009.7±11.9	101.18	10013.2±2.76	99.48
ILA	20	1104.7± 2.28	100.37	1107.7±6.99	100.60
	30	1686.42±1.42	102.67	1684.32±2.83	102.47
	40	2173.24±3.66	99.37	2170.75±0.71	99.26

Table 4: Repeatability studies on RP-HPLC for Levosulpiride and Ilaprazole Accuracy

RP-HPLC Method	Conc. of LEVO and ILA (mg/ml)	Peak area	Amount found (mg)	% Amount found
LEVO	300	10068.66	299.86	99.95
	300	10051.52	298.53	99.84
		Mean	10060.06	99.92
		SD	12.07	12.07
		%RSD	0.12	0.12
ILA	40	2184.07	39.91	99.77
	40	2180.045	39.82	99.53
		Mean	39.86	99.65
		SD	2.85	2.85
		%RSD	0.1307	0.13

Recovery studies were performed to validate the accuracy of developed method. To pre-analysed tablet solution, a definite concentration of standard drug (80%, 100%, and 120%) was added and then its recovery was analyzed. Statistical validation of recovery studies shown in Table 5 and 6.

Table 5: Result of Recovery data for Levosulpiride and Ilaprazole

Drug	Level (%)	Amt. taken (µg/ml)	Amt. Added (µg/ml)	Absorbance Mean* ± S.D.	Amt. recovered Mean ±S.D.	%Recovery Mean *± S.D.
LEVO	80%	75	60	136.6±0.05	61.58±0.05	102.64±0.08
	100%	75	75	151.9±0.50	76.9±0.50	102.5±0.66
	120%	75	90	164.91±0.29	89.81±0.29	99.90±0.32
ILA	80%	10	8	17.98±0.02	7.98±0.02	99.86±0.25
	100%	10	10	20.12±0.02	20.58±0.02	101.22±0.28
	120%	10	12	22.21±0.22	20.58±0.22	101.78±1.84

*mean of each 3 reading for RP-HPLC method

Table 6: Statistical Validation of Recovery Studies Levosulpiride and Ilaprazole

Level of Recovery (%)	Drug	Mean % Recovery	Standard Deviation*	% RSD
80%	LEVO	102.64	0.08	0.08
	ILA	99.86	0.25	0.25
100%	LEVO	102.5	0.66	0.33
	ILA	101.52	0.28	0.27
120%	LEVO	99.90	0.32	0.32
	ILA	101.78	1.84	1.81

*Denotes average of three determinations for RP-HPLC

Specificity:
The specificity of an analytical method is defined as the ability of a method to ensure that the peak(s) of interest elute as distinct responses in the presence of excipients, impurities or degradation compounds.

Robustness:
To evaluate robustness few parameters were deliberately varied. The parameters include variation of flow rate, percentage of methanol as described in Table 7.

Table 7: Robustness Evaluation of The HPLC Method

Chromatographic Conditions	LEVO			ILA		
	Tailing (T')	Capacity Factor (K')	Theoretical Plate (N)	Tailing (T')	Capacity Factor (K')	Theoretical Plate (N)
A: Mobile phase pH						
3.0	1.26	1.23	2683.9	1.28	0.99	7591.4
3.2	1.22	1.27	2683.5	1.23	1.09	7632.5
3.	1.21	1.33	2625.5	1.25	1.15	7414.7
Mean ±SD	1.23±0.02	1.27±0.05	2687.63±36.80	1.25±0.02	1.07±0.02	7546.2±115.7
B: Flow rate (ml/min.)						
0.5 ml	1.23	0.98	2723.8	1.26	0.76	7587.3
0.7 ml	1.16	1.08	2818.9	1.29	1.10	7668.8
1.0 ml	1.15	1.09	2768.7	1.22	0.88	7423.5
Mean ±SD	1.18±0.04	1.05±0.06	2770.47±47.50	1.25±0.03	0.91±0.17	7593.2±75.82
C: Percentage methanol in mobile phase (v/v)						
60	1.09	1.22	2646.2	1.18	0.87	7623.8
70	1.06	1.13	2687.4	0.94	0.95	7667.3
80	1.19	1.18	2638.3	1.23	0.87	7433.2
Mean ±SD	1.11±0.06	1.17±0.04	2657.3±26.36	1.11±0.15	0.89±0.04	7574±124.51

Study of system suitability parameters

The system suitability is used to verify, whether the resolution and reproducibility of the chromatographic system are adequate for analysis to be done. The test was performed by collecting data from five replicate injections of standard solution as shown in Table 8.

Table 8: System suitability test

LEVO		ILA	
System suitability parameters	Proposed method	System suitability parameters	Proposed method
Retention time (Rt)	2.9333	Retention time (Rt)	6.9167
Capacity factor (K')	1.18	Capacity factor (K')	0.98
Theoretical plate (N)	2838.7	Theoretical plate (N)	7465.8
Tailing factor (T)	1.16	Tailing factor (T)	0.95

Forced Degradation Studies

Forced degradation study was performed to evaluate the stability of the developed method using the stress conditions like exposure of sample solution to acid, base, Hydrogen peroxides (H_2O_2) and Neutral. Investigations were done for the degradation products in different conditions and are shown in Table 9.

Procedure for LEVO and ILA degradation

Acid hydrolysis
The acid hydrolysis performed using 0.1N HCl at 70 °C for 1st hr and 2nd hr for both LEVO and ILA indicated degradation. The major degradation products for LEVO and ILA were observed at relative retention time (RRT) for 1st and 2nd Hours.

Alkaline hydrolysis
The alkaline hydrolysis condition was performed using 0.1N NaOH at 70 °C for 1st hr and 2nd hr both LEVO and ILA. The major degradation products for LEVO and ILA were observed at relative retention time (RRT) for 1st and 2nd Hours.

Oxidation
In the oxidation condition with 3% H_2O_2 for 1st hr and 2nd hr both LEVO and ILA show oxidative stress degradation peak in the chromatogram.

Neutral
There was no major degradation observed for both LEVO and ILA and hence they were not sensitive to light at 70 °C for 1st hr and 2nd hr.

Table 9: Forced Degradation

Sample Exposure condition	Total Number of products with their Rt	LEVO		ILA	
		Degradation remained (150 µg/ml)	Recovery (%)	Degradation remained (30 µg/ml)	Recovery (%)
Acidic, 1N, 1 Hr	5 (2.95, 4.80, 6.05, 7.08, 7.65)	136.224	90.81	28.25	94.18
Basic, 1N, 1 Hr	6 (2.61, 2.80, 2.95, 3.38, 4.51, 7.20)	122.22	81.48	13.28	44.29
Per oxide, 30%, 1 Hr	4 (2.63, 2.83, 4.76, 7.03)	128.50	85.67	20.92	69.73
Heat, 50°C, 1 Hr	3 (2.61,2.81,6.766)	136.58	91.05	22.20	74.01

Application of analytical method

To determine the content of LEVO and ILA in marketed tablets (Brand: Blokcid L tablet labelled claim Levosulpiride 75 and Ilaprazole 10 mg make Ipca laboratories Ltd), 20 tablets powder weighed as 5.96 gm and average weight of powder was calculated in 0.298 gm (Elder, D. P., 2013). Tablets were triturated and powder equivalent to weighed in 298 mg. The drug was extracted from the tablet powder with 10 ml Methanol. To ensure complete extraction it was sonicated for 15 min. 0.1 ml of supernatant was then diluted up to 10 mL with mobile phase. The resulting solution was injected in HPLC and drug peak area was noted (Jain, N., 2008).

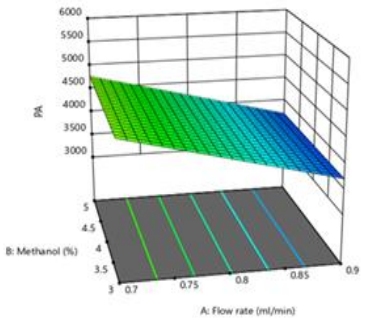
Results and Discussion

Such analytical methods are, in fact, an indicator of a quality product and the robustness of that product for the duration on the lifecycle of that product. The main goal of any HPLC method is to separate and quantitate analyte(s) of interest from any impurity and/or excipients (Surve S., 2013). Initially it is important to establish the critical quality attributes (CQA) of a system that may impact the quality of the analytical method (Pannu, S., 2022). Development of Analytical RP-HPLC Method with Design Space and Control Strategy determination by optimization study all the computations for the current optimization study and statistical analysis were performed using Design Expert® software (Design Expert trial version). State-Ease Inc., Minneapolis, MN, USA) (Kumar, R., 2017).

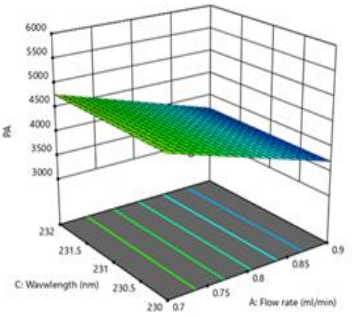
Application of design of experiments for method optimization Design of experiments (DOE-1)

Thus, 3 randomized response surface designs with a full fraction design were used with 17 trial runs to study the impact of three factors on the three key response variables. In this design 3 factors were evaluated, each at 3 levels, and experimental trials were performed at all 3 possible combinations. The mobile

phase composition (X1), Wavelength (X2) and flow rate (X3), were selected as independent variables and retention time (RT) and Resolution were selected as dependent variables (Avhad, P. S., 2022). The resulting data were fitted into Design Expert 10 Software and analyzed statistically using analysis of variance (ANOVA) and F-Test. Fig. 3 indicates the normal plot of residuals for retention time with other chromatographic parameters (Gaikwad, N. M., 2022). The data were also subjected to 3-D response surface methodology to determine the influence of flow rate, Wavelength and mobile phase composition on dependent variables as shown in Fig. 4. The probable trial runs using 3^3 full fraction designs are as shown in Table 4. Further ANOVA and F-test with variables are shown in Table 10-14. More over degradation peaks of API were shown in Fig. 5-8 from acidic, alkaline, peroxide and Heat (Tol, T., 2020, Pawar, S. S., 2022).



Contour plot depicting for X1= flow rate, X2= Methanol with wave length



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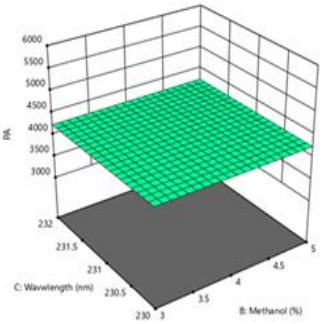

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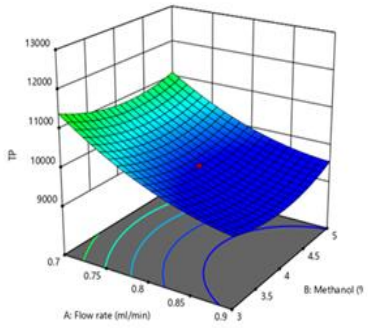
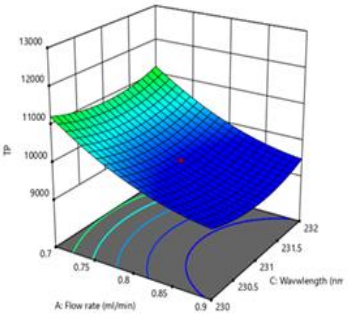
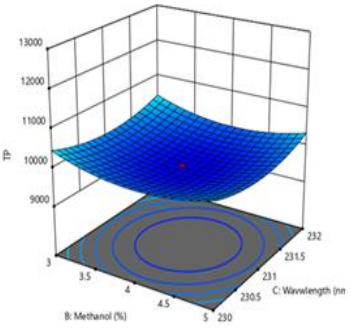


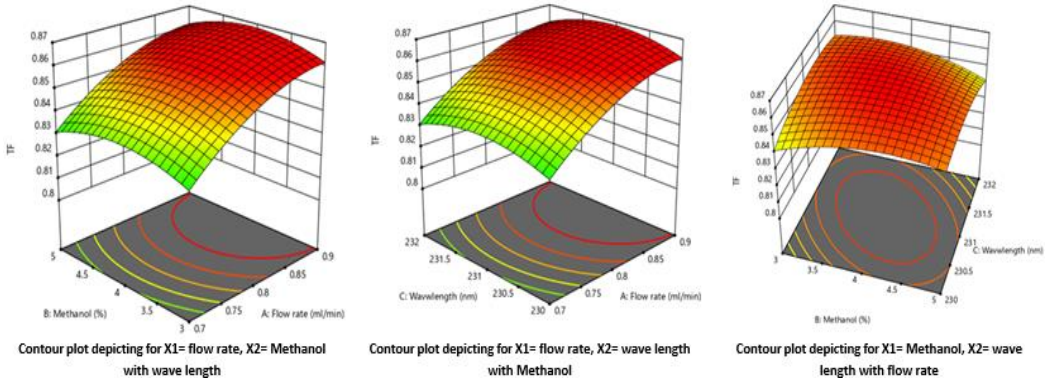
Contour plot depicting for X1= flow rate, X2= Methanol with wave length



Contour plot depicting for X1= flow rate, X2= wave length with Methanol



Contour plot depicting for X1= Methanol, X2= wave length with flow rate



Contour plot depicting for X1= flow rate, X2= Methanol with wave length

Contour plot depicting for X1= flow rate, X2= wave length with Methanol

Contour plot depicting for X1= Methanol, X2= wave length with flow rate

Fig. 4: Contour plot for flow rate, mobile phase composition and Wave Length

Table 10: Probable trial runs using 3^3 full fraction designs

Std	Run	Factor 1	Factor 2	Factor 3	Response 1	Response 2	Response 3	Response 4
		A:Flow rate	B:Methanol	C:Wave length	RT	PA	TP	TF
		ml/min	%	Nm				
1	1	0.7	3	230	3.45	4850.37	11675	0.82
11	2	0.8	2.3	231	2.95	4019.71	10892	0.84
5	3	0.7	3	232	3.369	4521.28	11693	0.83
9	4	0.6	4	231	3.89	5516.24	12789	0.8
3	5	0.7	5	230	3.33	4896.5	11458	0.83
6	6	0.9	3	232	2.61	3555.04	9810	0.86
7	7	0.7	5	232	3.32	4665.06	11373	0.82
13	8	0.8	4	229.3	2.92	4373.36	10645	0.84
2	9	0.9	3	230	2.62	3755.37	9777	0.85
10	10	0.8	4	231	2.62	3707.75	9733	0.86
4	11	0.9	5	230	2.71	4018.88	9950	0.86
8	12	0.9	5	232	2.69	3785.56	9793	0.85
12	13	0.8	5.7	231	3	4326.7	10679	0.84
14	14	0.8	4	232.7	3	4484.22	10716	0.84

Table 11: Anova for reduced quadratic model (response 1: RT)

Source	Sum of Squares	df	Mean Square	F-value	p-value	
Model	1.95	7	0.2783	211.69	< 0.0001	significant
A-Flow rate	1.10	1	1.10	833.33	< 0.0001	
B-Methanol	0.0005	1	0.0005	0.4083	0.5464	
C-Wavelength	0.0000	1	0.0000	0.0124	0.9149	
AB	0.0144	1	0.0144	10.93	0.0163	
A^2	0.1479	1	0.1479	112.53	< 0.0001	
B^2	0.0882	1	0.0882	67.09	0.0002	
C^2	0.0810	1	0.0810	61.60	0.0002	
Residual	0.0079	6	0.0013			
Cor Total	1.96	13				

Table 12: Anova for reduced linear model (response 2: PA)

Source	Sum of Squares	df	Mean Square	F-value	p-value	
Model	3.294E+06	1	3.294E+06	57.63	< 0.0001	significant
A-Flow rate	3.294E+06	1	3.294E+06	57.63	< 0.0001	
Residual	6.858E+05	12	57151.71			
Cor Total	3.979E+06	13				

Table 13: Anova for reduced quadratic model (response 3: TP)

Source	Sum of Squares	df	Mean Square	F-value	p-value	
Model	1.120E+07	7	1.600E+06	288.01	< 0.0001	significant
A-Flow rate	6.682E+06	1	6.682E+06	1202.92	< 0.0001	
B-Methanol	40072.40	1	40072.40	7.21	0.0363	
C-Wavelength	358.64	1	358.64	0.0646	0.8079	
AB	60031.13	1	60031.13	10.81	0.0167	
A^2	7.371E+05	1	7.371E+05	132.68	< 0.0001	
B^2	7.252E+05	1	7.252E+05	130.54	< 0.0001	
C^2	5.848E+05	1	5.848E+05	105.27	< 0.0001	
Residual	33330.78	6	5555.13			
Cor Total	1.123E+07	13				

Table 14: Anova for reduced quadratic model (response 4: TF)

Source	Sum of Squares	df	Mean Square	F-value	p-value	
Model	0.0040	7	0.0006	646.40	< 0.0001	Significant
A-Flow rate	0.0020	1	0.0020	2334.61	< 0.0001	
B-Methanol	0.0000	1	0.0000	0.0000	1.0000	
C-Wavelength	0.0000	1	0.0000	0.0000	1.0000	
BC	0.0002	1	0.0002	228.17	< 0.0001	
A^2	0.0004	1	0.0004	427.66	< 0.0001	
B^2	0.0003	1	0.0003	298.35	< 0.0001	
C^2	0.0003	1	0.0003	298.35	< 0.0001	
Residual	5.259E-06	6	8.765E-07			
Cor Total	0.0040	13				

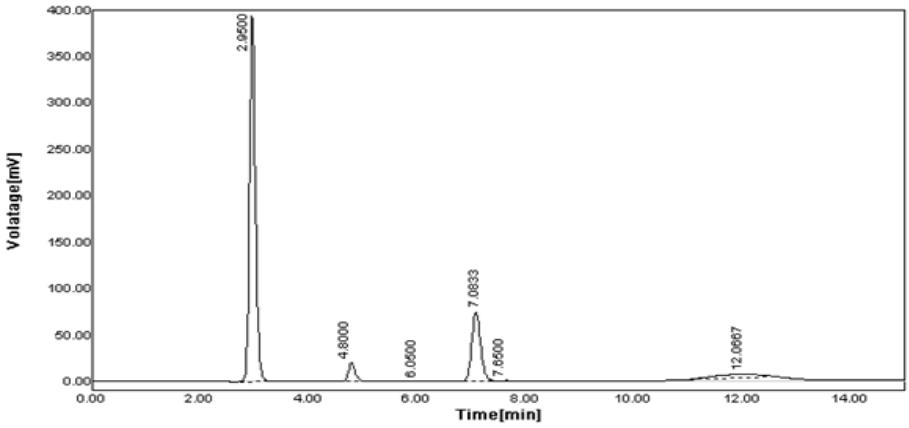


Fig. 5: Acidic degradation

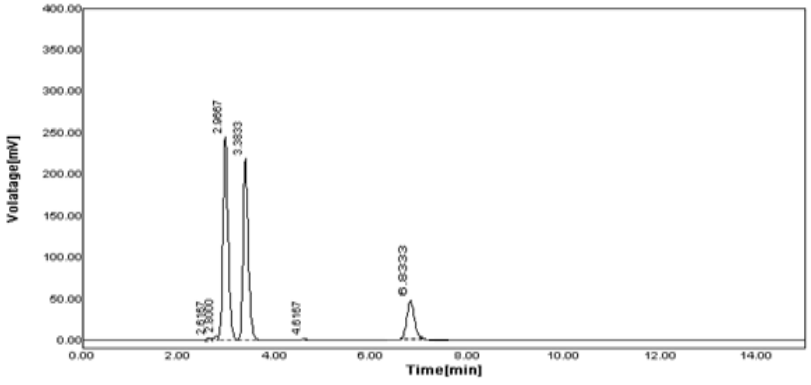


Fig. 6: Alkaline degradation

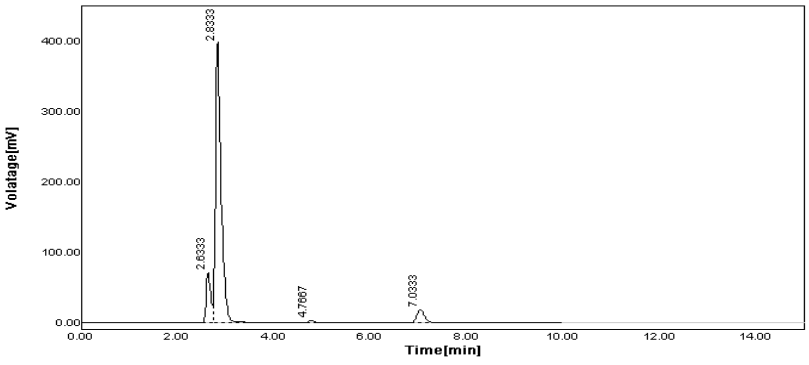


Fig. 7: Per oxide degradation

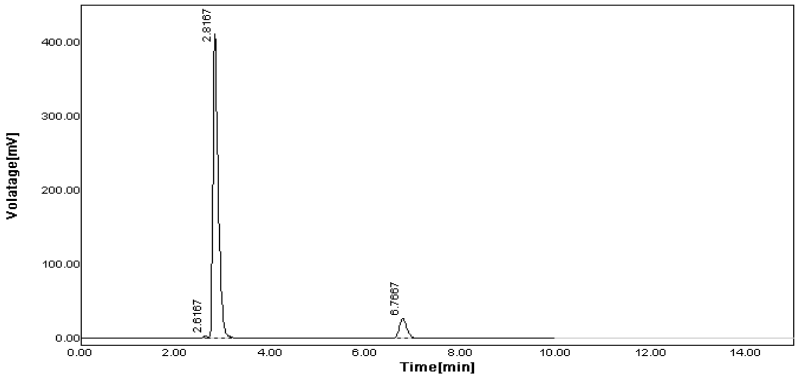


Fig. 8: Heat degradation

Conclusion

A simple, rapid, reliable, robust and optimized reversed phase high performance liquid chromatographic method for estimation of Levosulpiride and Ilaprazole was successfully developed and validated as per International Conference on Harmonization guidelines. Percentage of mobile phase, flow rate and wave length were optimised by using QbD approach *i.e.* 3^3 factorial design. There are no interfering peaks in performed degradation conditions. Therefore, a sensitive, accurate and stability indicating method was developed with high degree of practical utility.

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