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Optimization technique as a tool for implementing analytical quality by Design

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Abstract: A process is well understood when all critical sources of variability are identified and explained, variability is managed by the process, and product quality attributes can be accurately and reliably predicted over the design space. Quality by Design (QbD) is a systematic approach to development of products and processes that begins with predefined objectives and emphasizes product and process understanding and process control based on sound science, statistical methods and quality risk management. In an attempt to curb rising development costs and regulatory barriers to innovation and creativity, the FDA and ICH have recently started promoting QbD in the pharmaceutical industry. QbD is partially based on the application of statistical Design of Experiments strategy to the development of both analytical methods and pharmaceutical formulations. The present work describes the development of robust HPLC method for analysis of Eplerenone formulation under QbD approach using Design of Experiments.

Keywords: Quality by Design, Design of Experiments, Quality Risk Management, Product and Process Quality Attributes.

INTRODUCTION:

Analytical methods are developed at various stages of the drug development process for samples of varying complexity. Development of analytical methods for high performance Liquid Chromatography (LC) instrument systems is typically carried out in three phases. The phase I involves major effectors of selectivity, primarily the column chemistry, buffer pH, and organic mobile phase. Formal method development, the phase II, involves experimenting with additional instrument parameters believed to strongly affect compound separation like pump flow rate, final percent organic, and column temperature. Phase III involves the verification/confirmation of the Method Parameters[1].The overall goal of the three phases is identification of the instrument parameter settings that provide optimum chromatographic performance. This article describes how statistically rigorous Quality-by-Design (QbD) principles can be put into practice to accelerate each phase of LC instrument method development. The experimental runs were conducted according to Plackett Burman design and 2-level Factorial designs[2]. Under Plackett Burman design, factors such as Column type, Buffer pH and Organic phase were screened and under 2- level Factorial design, factors such as Flow Rate, Column Temperature and Final Percent Organic were optimized[3]. The optimized method can be used for routine analysis of Eplerenone tablets in Quality control laboratories.

MATERIALS AND METHODS:

Details of Drug Product:

Generic Name of the Product	Eplerenone
Dosage form	Film coated Tablets
Label Claim	50 mg

Table 1: details of drug product

Chemicals Used:

S. No.	Chemicals or Reagents	Make
1	Methanol (HPLC grade)	Rankem
2	Acetonitrile (HPLC grade)	Rankem
3	Milli-Q Water	TKA
4	Ortho-phosphoric acid (HPLC grade)	Rankem

Table 2: List of chemicals used

Instrument Specifications

S. No.	Name	Model	Make	Software
1.	Micro Balance	MX5	Mettler Toledo	-
2.	Analytical Balance	AUW220D	Shimadzu	-
3.	pH Meter	-	Eutech Instrument	-
4.	Centrifuge	-	S V Scientific	-
5.	Ultra Sonicator	-	S V Scientific	-
6.	UV Spectrophotometer	PharmaSpec UV- 1700	Shimadzu	UV Probe 2.10
7.	HPLC	Agilent	1200 series	Chemstation
8.	Detector: UV-Visible / PDA Detector	2498 UV-Visible 2998 PDA	Waters	-

Table 3: Instruments Used During the Method Development

Method Development:

A new RP-HPLC method was developed for the determination Eplerenone by using Design of Experiment software. The HPLC method was then validated to indicate that the analytical procedure used is suitable for intended use by using various parameters like specificity, linearity, precision, accuracy, range, robustness, stability in analytical solution, system suitability and filter interference[4].

A Quality By Design with Design of Experiments approach to the development of an analytical method mainly involves three phases[5]

PHASE I: Rapid Screening

PHASE II: Method Optimization.

PHASE III: Verification/Confirmation

PHASE I: Rapid Screening

The first phase of the method development involves the screening of the major effectors of selectivity, primarily the column chemistry, buffer pH, and organic mobile phase[6]. The variables and ranges screened along with the constant conditions are listed in the table below (table 4).

FACTORS/VARIABLES	RANGES
Column type	Waters symmetry / sunfire
Buffer pH	Phosphate Buffer 3.2 / 6.5
organic Phase	Acetonitrile/ Methanol

Table 4: Factors and their ranges (levels)

The above factors are optimized using design of experiment software such as MINITAB, DESIGN EXPERT, ECHIP, JMP etc. Here MINITAB software was used for the purpose[7].

There were number of designs to evaluate the above factors such as Screening Designs, Factorial Designs, Mixture Designs, and Response surface Designs [8]. For phase I factors, Screening designs (such as Plackett Burman) were used.

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Run Order	column type	Buffer pH	Organic phase	Retention time	Theoretical plates	Tailing Factor
1	sunfire	3.2	Methanol	10	2500	1.8
2	waters symmetry	3.2	Acetonitrile	9.06	5997	1.04
3	waters symmetry	6.5	Acetonitrile	9.2	5400	1.38
4	waters symmetry	6.5	Methanol	10.1	3000	1.54
5	sunfire	6.5	Acetonitrile	9.6	2000	1.76
6	sunfire	3.2	Acetonitrile	9.4	2300	1.53
7	waters symmetry	3.2	Acetonitrile	9.1	5082	1.01
8	sunfire	6.5	Methanol	10.2	1876	1.69
9	waters symmetry	6.5	Methanol	10.19	3245	1.38
10	sunfire	6.5	Acetonitrile	9.55	2100	1.49
11	sunfire	3.2	Methanol	9.9	1748	1.38
12	waters symmetry	3.2	Methanol	10.3	2678	1.33

Table 5: Trail runs with responses

The responses obtained after carrying out trail runs were feeded back to DOE software and the Main Effects Plots andCube Plots of Theoretical Plates (TP), Retention Time (RT), Tailing Factor (TF) were plotted.

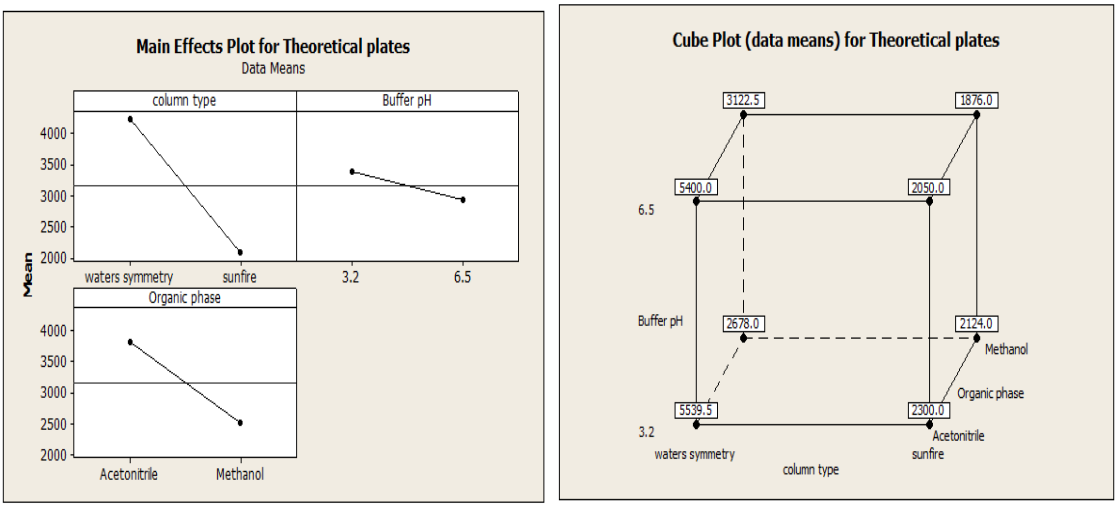

Fig 1: Main Effects Plots and Cube Plots for Theoretical Plates

Observation: From the above figure (fig 1), it indicates that Theoretical Plates are more when Waters Symmetry Column, Phosphate Buffer pH3.2 and Acetonitrile were used in comparison to Sunfire Column, Phosphate Buffer pH6.5 and Methanol respectively.

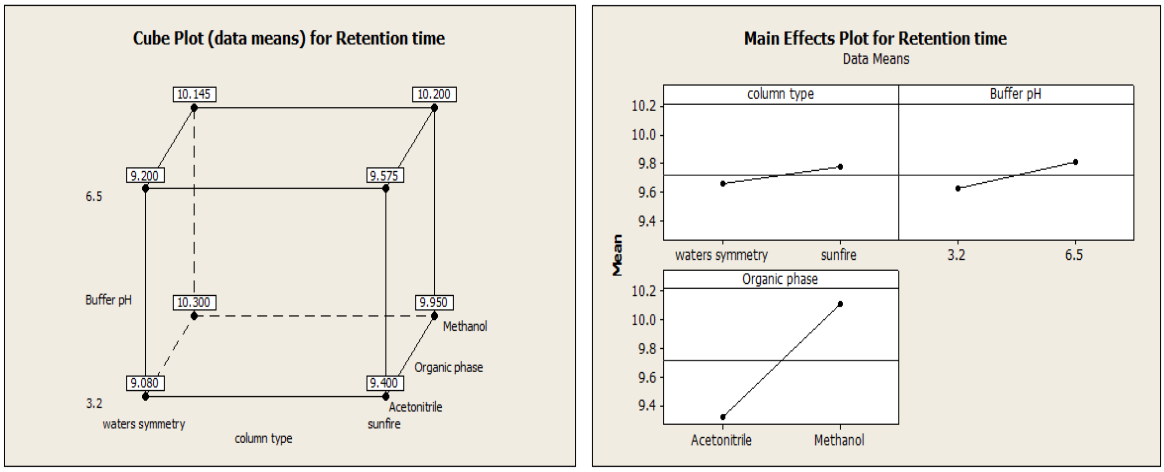

Fig 2: Main Effects Plots and Cube Plots for Retention Time

Observation: From the above figure (fig 2), it indicates that Retention Time is less when Waters Symmetry column, Phosphate Buffer pH 3.2 and acetonitrile were used in comparison to Sunfire Column, Phosphate Buffer pH6.5 and Methanol respectively.

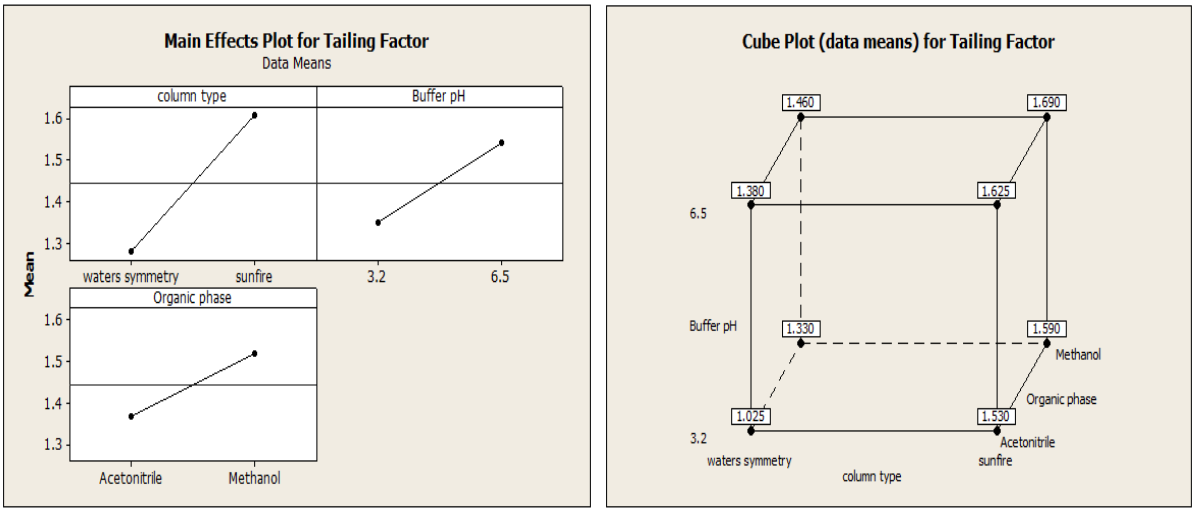

Fig 3: Main Effects Plots and Cube Plots for Tailing Factor

Observation: From the above figure(fig 3), it indicates that Tailing Factor is less when Waters Symmetry Column, Phosphate Buffer pH3.2 and Acetonitrile were used in comparison to Sunfire Column, Phosphate Buffer pH6.5 and Methanol respectively.

Conclusion: Based on the above Main Effects Plots and Cube Plots for Tailing factor, Retention Time and Theoretical Plates, Waters Symmetry column, Phosphate Buffer pH 3.2 and Acetonitrile were selected.

PHASE II: Method Optimization

Phase II experiments use the Column Type, Buffer and Mobile phase results from phase I plus additional variables with tighter ranges to determine the optimum method[9]. The experiment design is created using pump flow rate, final % organic, and column temperature as final optimization variables in the ranges given below (table 9).

FACTORS/VARIABLES	RANGES
Flow rate	1.0 to 1.5
Column temperature	20 ^{O}C to 40 ^{O}C
Final % organic	30% to 70 %

Table 6: Phase II Factors and their ranges (levels)

For phase II factors, Factorial Design) were used as there is linearity between Factors and the Response.

Trail Runs with Responses:

Trial Run Order	Flow Rate	Column Temp	Final % Organic	Retention Time	Theoretical Plates	Tailing Factor
1	1	20	70	2.6	7398	1.38
2	1	20	30	11	5997	1.79
3	1.5	40	30	9.8	1748	1.38
4	1.5	40	70	1.72	5061	1.33
5	1	40	70	2.61	6425	1.4
6	1	40	30	11.3	1692	1.42
7	1.5	20	70	1.81	5082	1.3
8	1.5	20	30	9	1876	1.9

Table 7: Trail runs with Responses

The responses obtained after carrying out trail runs were feeded back to DOE software and the Contour Plots of Theoretical Plates (TP), Retention Time (RT), Tailing Factor (TF) were plotted.

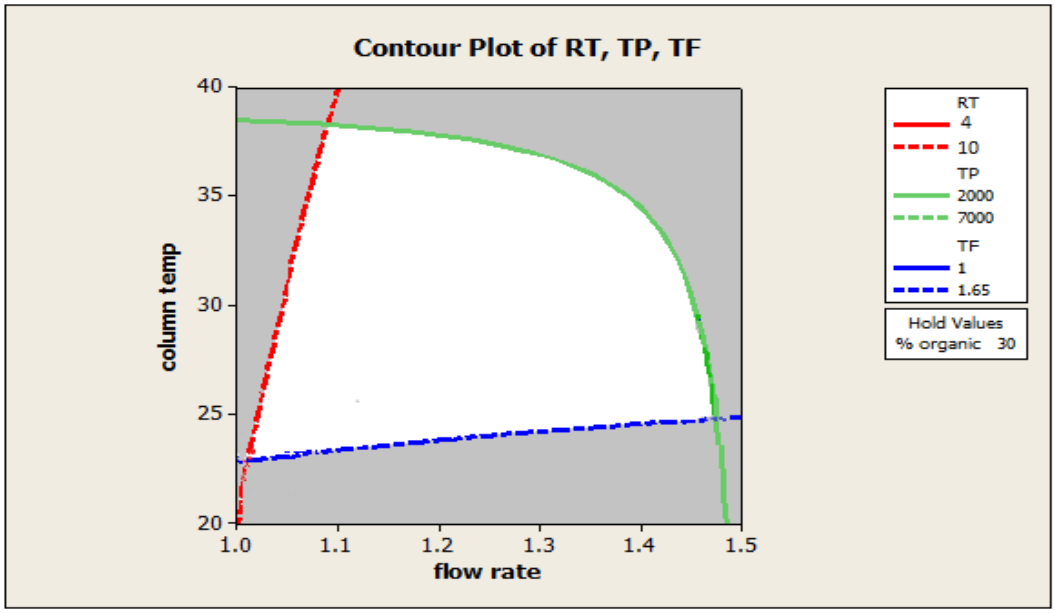

Fig 4: Overlaid Contour Plots for Retention Time, Theoretical Plates and Tailing Factor against Column Temperature and Flow rate

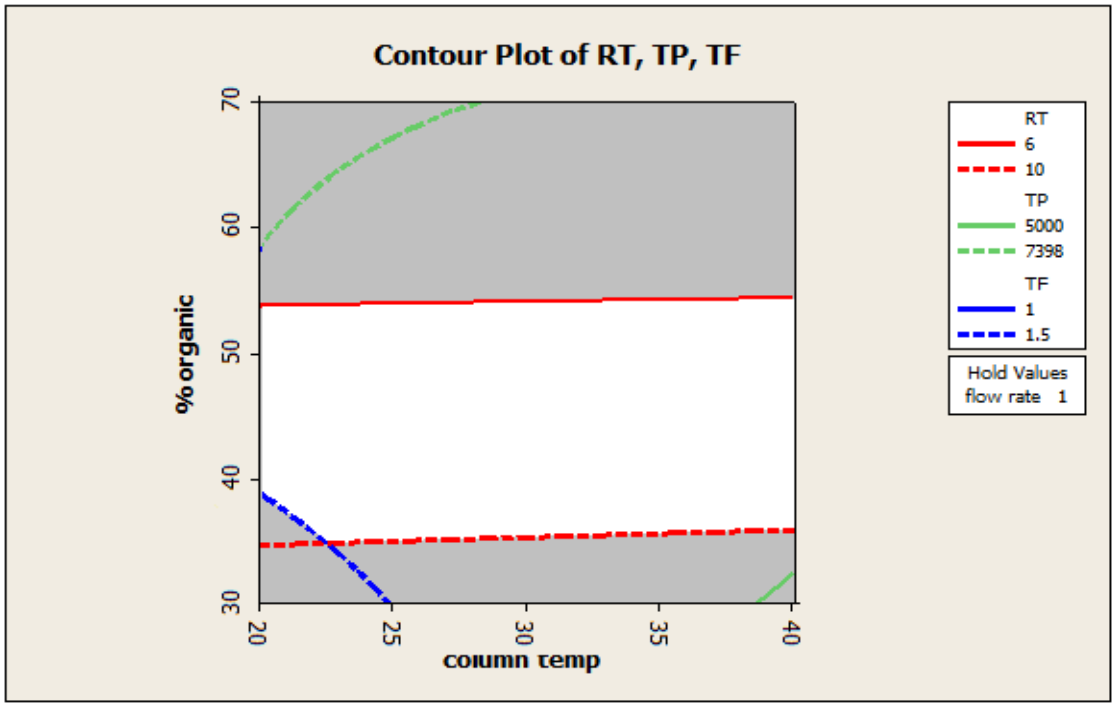

Fig 5: Overlaid Contour Plots for Retention Time, Theoretical Plates and Tailing Factor against Column Temperature and % Organic phase

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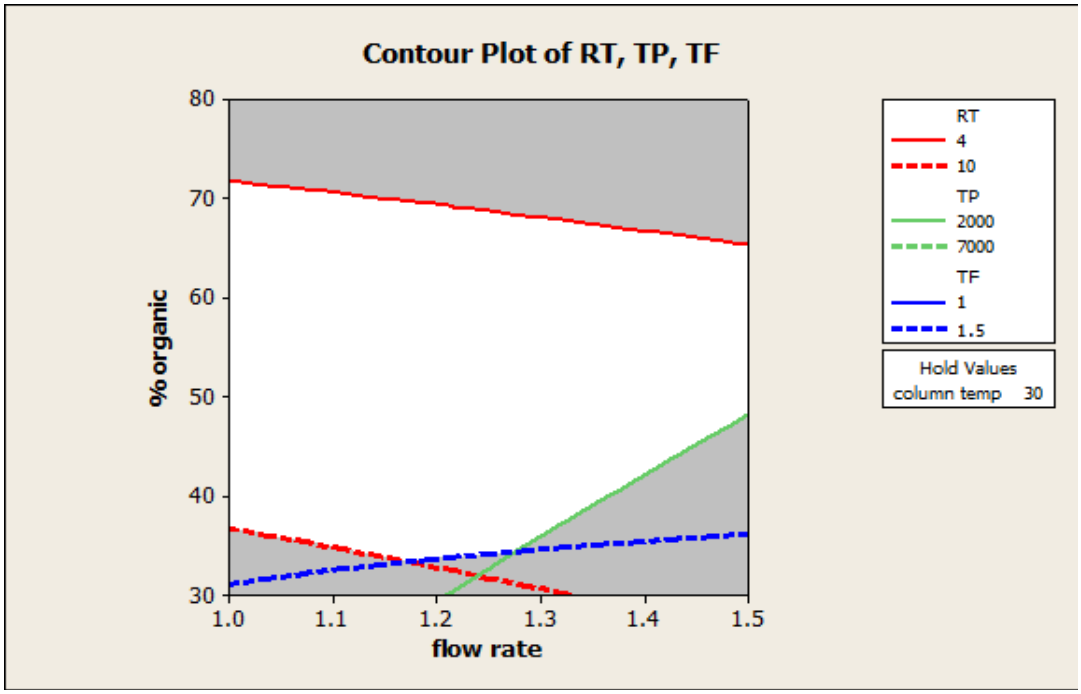

Fig 6: Overlaid Contour Plots for Retention Time, Theoretical Plates and Tailing Factor against % Organic phase and Flow rate

The unshaded region in the above plots (fig 4,5,6) indicates the design space where all the responses are feasible.The overlaid Contour Plots shows the QBD Design Space (unshaded region) where the method meets the mean performance goals and robustness criteria.

Using related response variables, the method optimizer determines the optimum method to best meet the performance and robustness goals specified. The final method conditions are listed along with predicted response results.

Optimization Plot:

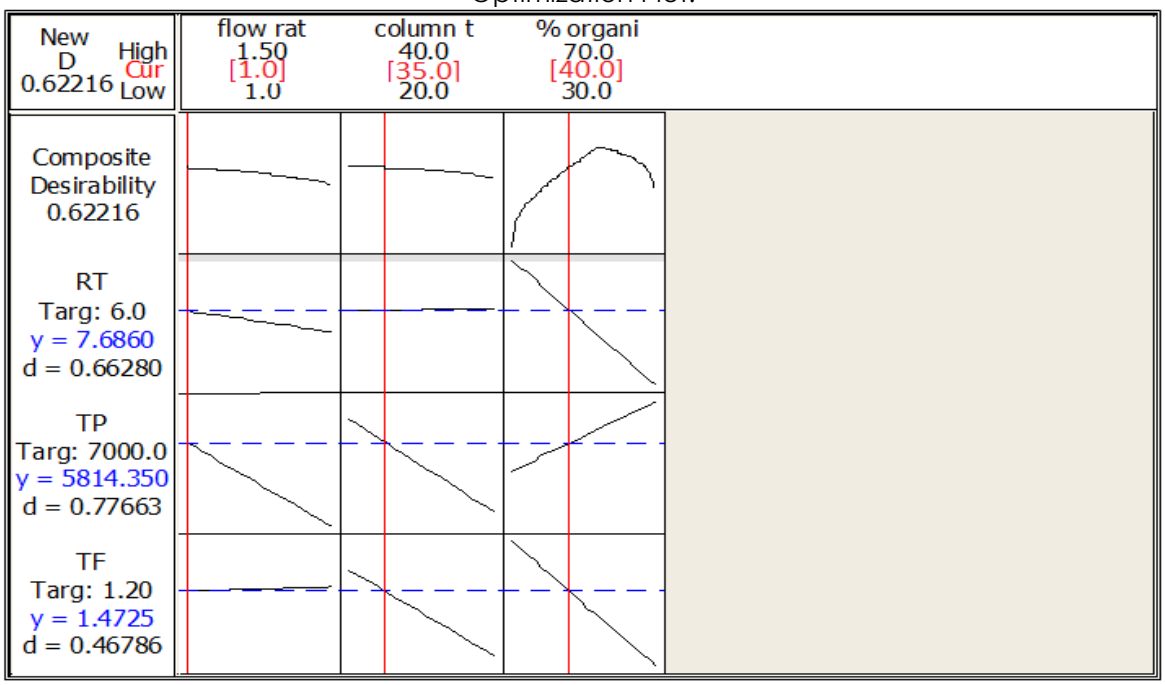

Fig 7: Final Optimization Plot

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Conclusion: The above plot (fig 7) indicates that at Flow rate of 1.0 ml/min, Column Temperature of 35 oC and % Organic phase of 40 % will give the required target.

RESULTS AND DISCUSSION:

Optimized Results:

The Optimum Method determined by the Minitab Response Optimizer was:

Column:	waters, symmetry, c18 (250 mm X 4.6 mm X 5µm)
Flow rate:	1.0 ml/min
Wavelength:	220nm
Detector:	PDA detector
Injection volume:	10µl
Mobile Phase:	Acetonitrile: phosphate buffer ph 3.2 (60:40)
Column oven temperature:	35°C
Run time:	15min

Table 8: Optimization Results

The method was exported to chemstation and the sample was run to evaluate the prediction accuracy.

PHASE III: Verification/Confirmation

Method Validation:

The objective is to validate the Method for Assay of Eplerenone in Eplerenone 50 mg tablets. This report presents and discusses the results obtained in the validation study for the parameters namely System suitability, Precision, Specificity, Linearity, Accuracy, Stability of solution, Robustness and Filter validation of the test method [10, 11].

Validation Parameter	Acceptance Criteria	HPLC Results
System Suitability	The RSD should be NMT 2.0% for 6 replicate injections for each peak	0.4
Accuracy	The % Recovery at each spike level shall be NLT 98.0.0% and NMT 102.0.0% of the added amount.	98.5
System Precision	The % RSD of peaks obtained from the 6 replicate injections should be NMT 1.0%	0.4
Method precision	The % RSD for the six determinations shall be NMT 2.0%	1.0
Specificity	The peaks of diluent and placebo should not interfere with the main peak	The peaks of diluent and placebo are not interfering with the main peaks of Eplerenone
Linearity	The Correlation coefficient shall be NLT 0.995	0.9999
Robustness	All the system suitability parameters should pass for all the conditions.	The system suitability parameters passed for all the conditions
Ruggedness	All the system suitability parameters should pass for all the conditions.	The system suitability parameters passed for all the conditions

Table 9: Summary of Method Validation Parameters

CONCLUSION:

A simple and efficient reverse-phase HPLC method under QBD approach by using Design of Experiment (DOE) software was found to be accurate, precise, and linear across the analytical range. The method was found to be specific for the determination of Eplerenone in pharmaceutical formulations.

The experimental runs were conducted according to Plackett Burman and 2 level factorial designs. Under Plackett Burman design, factors such as column type, buffer pH and organic phase were screened and under 2 level factorial designs, factors such as Flow Rate,

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Column Temperature and Final Percent Organic were optimized. The obtained results were interpreted in statistical software (Minitab) and finally it is concluded that Mobile phase composition of 60:40, Flow rate of 1 ml/min, Column oven temperature of 35°C were found to be optimized

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