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# Development and Validation of telmisartan and Chlorthalidone in Bulk And Tablet using Quality by Design Approach

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**ABSTRACT**

*A novel, sensitive, appropriate, simple, precise and robust. For the detection of Telmisartan and Chlorthalidone in bulk medication and tablet, a reversed-phase high-performance liquid chromatography (RP-HPLC) technique was developed and validated. Method optimization was performed by response surface methodology with applying three-level Box-Behnken design. Based on these designed aspect, we were selected three factors such as mobile phase concentration, pH and flow rate. The separation and detection was carried out at wavelength 282nm using mobile phase 0.1% W/V Ortho-phosphoric acid (OPA): Acetonitrile (55:45%v/v) at 25⁰C. The mobile phase pH was adjusted at 2.5 ±0.05 by addition of Triethylamine (TEA). The flow rate of both drugs was selected 1.2mL/min. The retention time of Telmisartan and Chlorthalidone were 4.056 min and 2.011 min, respectively. The linearity of Telmisartan and Chlorthalidone was 10-50 µg/mL and 10-50 µg/mL, respectively. The correlation coefficient ($r^2$)of both drugs was found to be 0.999.Thepercentage relative standard deviation (RSD)was found to be lessthan2.0%.Thepercentagerecoveriesof Telmisartan and Chlorthalidone were found to be 98.04-101.36% and 99.25-101.45%, respectively. The detection limit (DL) and quantitation limit (QL) for Telmisartan and Chlorthalidone were found to be 1.82 ug/mL and 5.41 ug/mL, 1.88 ug/mL and 5.72 ug/mL, respectively. The optimized chromatographic method was validated as per ICH Q2 (R1) guidelines. The industry can use the established and validated RP-HPLC technology for quality control, analysis of bulk drugs, and marketed products of telmisartan and chlorthalidone because it is less time-consuming.*

***Keywords:****RP-HPLC, Telmisartan, Chlorthalidone, Analytical quality by design, Development,Validation*

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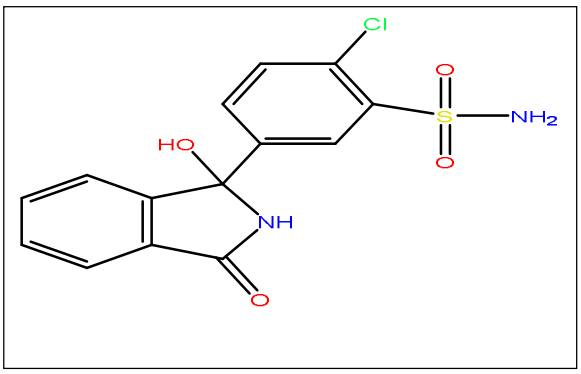
## INTRODUCTION

Telmisartan(TEL), chemically known as (4-{[4-Methyl-6-(1-methyl-1H-1, 3-benzodiazol-2-yl)-2-propyl-1H-1, 3-benzodiazol-1-yl] methyl} phenyl) benzoic acid(Figure 1). It is used as selective angiotensin-II type-1 receptor blocker that is essential for the treatment of hypertension[1-2].According to the findings of a retrospective study and based on real-world data obtained from electronic medical records, the angiotensin-converting enzyme, other hormone receptors and ion channels are not inhibited by [3]. In addition a number of studies were shown that, telmisartan may also act as a partial agonist of the PPAR-gamma receptor, which is a well-known target for diabetes medications. This shows that telmisartan may be more efficient in controlling insulin resistance while also improving carbohydrate and lipid metabolism without the side effects generally associated with complete PPAR-gamma activators.[4-7].

Chlorthalidone (CHLOR) is (RS) 2-chloro-5-91-hydroxy-3-oxo-2, 3-isoindo-1-yl) benzene1sulfonamide (Figure2),is a thiazide diuretic drug that is used for the treatment of hypertension as well as the management of edema induced by disorders such as heart failure or renal impairment. It has been FDA-approved for manage hypertension since the year 1960. Improves blood pressure and edema by inhibiting water absorption from the kidney by blockage of the $Na^+/Cl^-$symporter in the distal convoluted tubule cells in the kidney. It is a first-line medication for the treatment of hypertension[8-11].



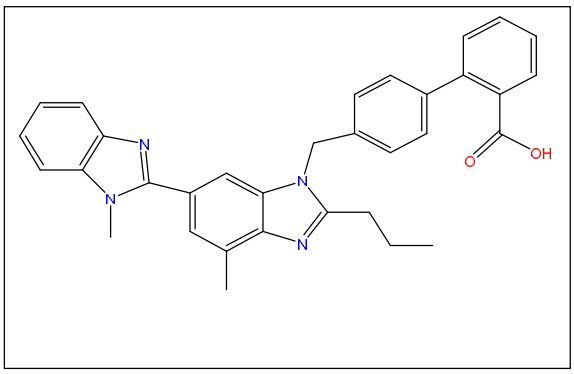




**Figure 1.** Chemical structure of Telmisartan **Figure 2.** Chemical structure of Chlorthalidone

According to a survey of the literature, quality by design has not been applied to UV-Visible spectroscopy or HPLC (QbD). Simple validated RP-HPLC methods for the estimation of TEL and CHLOR in pharmaceutical dosage forms must be established utilising the QbD approach in accordance with ICH Q8 (R2) standards to maintain process consistency throughout the product lifecycle. [12-15].

## MATERIAL AND METHODS

### Chemicals

TELwas obtained as a gift sample from Virchow Pvt. Ltd and CHLOR was provided as a gift sample from IPCA Pharmaceutical, Mumbai. HPLC grade water, methanol and acetonitrile was provided by Alpha chemicals Pvt. Ltd. Orthophosphoric acid and triethylamine was provided by college.

### Equipment

A Waters 1525 binary pump with Waters 2489 UV visible detector was used as a chromatographic system. Other instruments such as analytical pH meter (pH cal), Electronic weighing balance (AUX 220, Shimadzu), and Ultra Sonicator (Citizen UK) were also used.

### QbD software

Design expert software (Design expert trial version 13.0.5.0 64-bit, State-Ease Inc., Minneapolis, MN, USA).

Chromatographic conditions

As the stationary phase, an Inertsil C18 column (150 mm 4.5 mm 5 m) was employed. The mobile phase flow rate was 1.2 mL/min, the column oven temperature was maintained at 25°C, and the detection wavelength was 282 nm. The injection volume was 6 µL, and the retention time for TEL and CHLOR were 4.056 seconds and 2.011 seconds, respectively.

### Preparation of solutions

Selection of detection wavelength

Standard solution was scanned between 200-400 nm, TEL and CHLOR were found to have significant absorbance at wavelength 282 nm.

### Preparation of mobile phase

0.1% OPA was prepared by taking 0.1mL of OPA in 100 mL of volumetric flask and top up with water to reach the desired amount. Sonicated for 5 min after thoroughly mixing, pH was adjusted to 2.5 (± 0.05) with the diluted triethylamine solution.

### Preparation of standard stock and working standard

After carefully transferring an accurately weighed quantity of 10 mg of TEL and 10 mg of CHLOR into separate 10 mL volumetric flasks, 8 ml of methanol was added, sonicated to dissolve it, and then the volume was made up with methanol and mixed. These stock solutions had a concentration of 1000 µg/mL of TEL and 1000 µg/mL of CHLOR respectively. To get a final concentration of 100 g/mL of TEL and 100 g/mL of CHLOR, take 1 mL from each individual stock solution in the previous step, transfer it to a volumetric flask containing 10 mL, and then dilute it with methanol until it reaches the mark. From the above solutions, transfer 4 mL of TEL and 1.25 mL of CHLOR to a 10 mL volumetric flask. Then, dilute the mixture until it reaches the mark to get a concentration of 40 g/mL for TEL and 12.5 g/mL for CHLOR.

### Sample preparation

For the purpose of simultaneously estimating TEL and CHLOR in tablets (TELMIKIND-CT 40 label claims that the product contains 40 mg TEL and 12.5 mg CHLOR), twenty tablets were weighed, their average weight was obtained, and then the tablets were crushed into a fine powder. The powder containing an amount equivalent to 40 mg of TEL and 12.5 mg of CHLOR was transferred to a volumetric flask with a capacity of 50 mL, where it was dissolved in 25 mL of methanol, sonicated for 20 minutes, and then

diluted with methanol up to the mark to obtain 800 µg/mL of TEL and 250 µg/mL of CHLOR. After diluting 1 mL of the filtrate to a total volume of 10 mL with methanol, the final product contained 80 µg/mL of TEL and 25 µg/mL of CHLOR. In the end, 5 mL of this solution was diluted with methanol to a volume of 10 mL in order to obtain a concentration of TEL that was 40 µg/mL and a concentration of CHLOR that was 12.5 µg/mL. (Figure 3and 4) represents the typicalstandard and sample chromatogram of TEL and CHLOR.

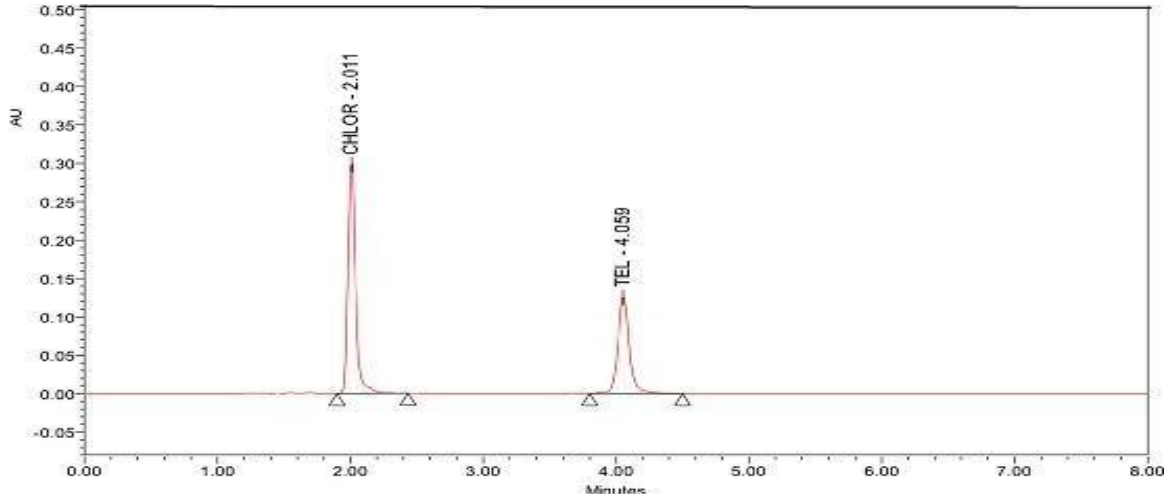



**Figure 3.** Standard chromatogram of TEL and CHLOR

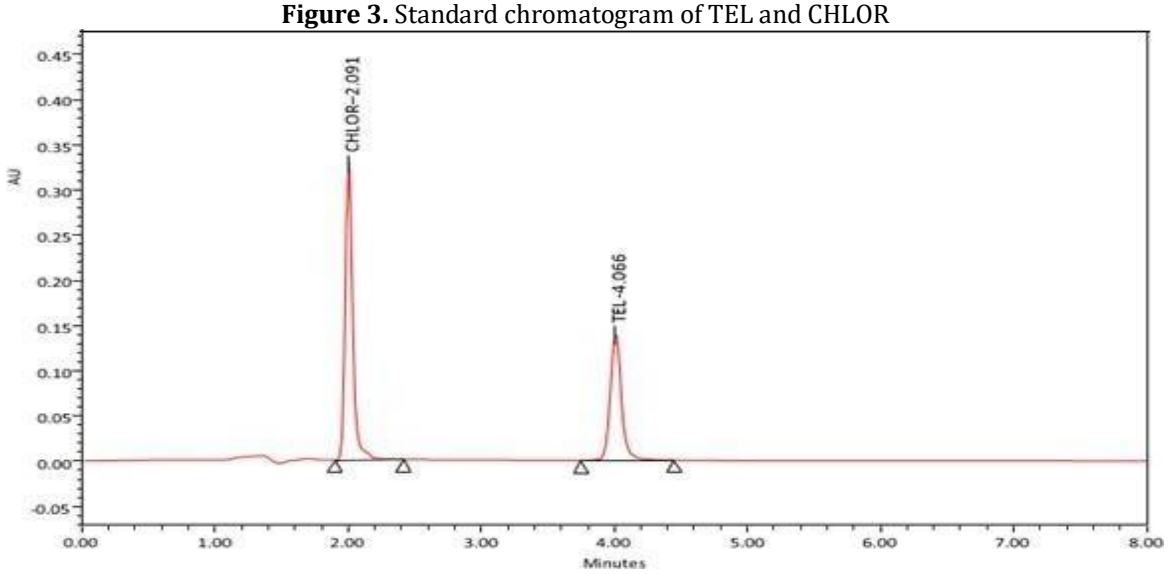



**Figure 4.** Sample chromatogram of TEL and CHLOR

**Application of design of experiment (DoE) for method optimization by QbD approach**

$3^3$ randomised response surface designs with a Box Behnken design were used in 17 trial runs to examine the effects of three factors on the three primary response variables.

Three parameters were investigated in this design, each at three levels, and experimental trials were conducted in all possible combinations. Based on risk analysis, mobile phase (X1), flow rate (X2) and pH (X3), composition were chosen as independent variables, while retention time-1 (RT-1), retention time-2 (RT-2) and Resolution were chosen as dependent variables. The data was then entered into Design Expert 13.0.5.064 software and statistically analysed using analysis of variance (ANOVA).The data was also subjected to 3D response surface methods to see how flow rate, pH, andmobile phase composition affected the dependent variables. The trial runs using $3^3$ Box Behnken design were shown in **Table 1**. The experimental result and optimized method conditions were incorporated in **Table 2**.

**Table 1.** $3^3$ Box-Behnken full factorial design

| STD Run | Factor1 A: Mobile phase | Factor2 B:pH | Factor3 C: flowrate | Response1 RT1 | Response2 RT2 | Response3 Resolution |
|---|---|---|---|---|---|---|
| 11 | 45 | 2.3 | 1.4 | 2.046 | 4.125 | 10.98 |
| 15 | 45 | 2.5 | 1.2 | 2.011 | 4.056 | 10.23 |
| 1 | 40 | 2.3 | 1.2 | 2.561 | 4.985 | 12.98 |
| 2 | 50 | 2.3 | 1.2 | 1.998 | 3.956 | 9.56 |
| 5 | 40 | 2.5 | 1 | 2.658 | 4.356 | 13.89 |
| 10 | 45 | 2.7 | 1 | 1.796 | 3.963 | 11.02 |
| 7 | 40 | 2.5 | 1.4 | 2.336 | 4.985 | 14.25 |
| 4 | 50 | 2.7 | 1.2 | 1.895 | 3.859 | 9.65 |
| 9 | 45 | 2.3 | 1 | 1.852 | 4.036 | 11.65 |
| 3 | 40 | 2.7 | 1.2 | 2.985 | 5.023 | 13.58 |
| 8 | 50 | 2.5 | 1.4 | 1.945 | 3.589 | 8.99 |
| 17 | 45 | 2.5 | 1.2 | 2.011 | 4.056 | 10.23 |
| 14 | 45 | 2.5 | 1.2 | 2.011 | 4.056 | 10.23 |
| 13 | 45 | 2.5 | 1.2 | 2.011 | 4.056 | 10.23 |
| 16 | 45 | 2.5 | 1.2 | 2.011 | 4.056 | 10.23 |
| 6 | 50 | 2.5 | 1 | 1.896 | 3.999 | 9.89 |
| 12 | 45 | 2.7 | 1.4 | 1.802 | 4.011 | 11.92 |

**Table 2.Experimental results and optimized method conditions**

| Parameters | Description |
|---|---|
| Program | Isocratic |
| Mobile phase | 0.1% OPA: Acetonitrile |
| Wavelength | 282 nm |
| Injection volume | 6µL |
| Flow rate | 1.2 mL/min |
| Run time | 8min |
| Column oven temperature | 25°c |

**Method Validation**

Using ICH Q2 (R1) guidelines, the developed method for predicting TEL and CHLOR was validated for the following parameters.

**System Suitability**

Six replicate injections of standard TEL and CHLOR at concentrations of 40 µg/mL and 12.5 µg/mL, respectively, were used to determine the repeatability, theoretical plates, tailing factor, and retention time, and the appropriate recommended values were calculated.

**Accuracy**

Prepare the standard solution by taking stock solution equivalent to 80%, 100%, and120%eachintriplicate.The percent recoveries of TEL and CHLOR in drug-matrix form were calculated for each concentration that was introduced into the HPLC system. Additionally, the accuracy was computed and evaluated using linear regression analysis.

**Linearity**

By diluting standard stock solution, linearity testing was carried out. Aliquots of 0.1, 0.2, 0.3, 0.4, and 0.5 mL from the stock solution were diluted to a final volume of 10 mL with diluent, resulting in final concentrations of TEL and CHLOR that ranged from 10 to 50 µg/mL and 10 to 50 µg/respectively. During the regression analysis, the average area of each concentration was taken into account. Plotting was done between the analyst concentration and the peak area. By computing the linear regression analysis, square correlation coefficient (R2), and % y-intercept, the linearity was evaluated.

**Precision**

There are two different levels of accuracy to choose from both repeatability (Intraday) and intermediate precision (Inter day) are required. It is performed through the API. The repeatability of the method was evaluated by doing an analysis of the formulation six times while maintaining the same concentration throughout. % RSD was determined.

**Detection**

The limit of detection (DL) and limit of quantitation (QL) were analyzed and determined using the following equation, which is dependent on the standard deviation of the y-intercept and the slope of the calibration graph.

DL = 3.3 SD/S, QL = 10 SD/S

## RESULTS AND DISCUSSION

### Method optimization

Preliminary experiments were conducted using a mobile phase made up of water and MeOH or ACN after selecting the appropriate diluents or solvents. TEL and CHLOR have pKa values of 4.45 and 9.4, respectively. Different ratios of ACN and MeOH were investigated along with OPA and phosphate buffers with different pH.To separate TEL and CHLOR, reverse phase columns of both longer and shorter C18 were utilised. However, shorter C18 was shown to have greater separation and a sharper peak. A 150 mm column length was selected to provide better separation between TEL and CHLOR. To determine the best retention time without reducing resolution, a variety of pH mobile phases were examined at flow rates between 0.8 and 1.5 mL/min.

To optimise the chromatographic conditions, the DoE tools were applied. Several parameters were identified as input variables throughout the experiment.

However, because they are important in the responses, the three potential parameters pH, organic ratio, and flow have been offered as input variables in the software. With the exception of RT and resolution, which appeared to be practical factors for this investigation, the majority of output responses exhibited only modest variation based on the selected factor. The method was optimised using a mobile phase containing 0.1% OPA and a pH adjustment of 2.5 by TEA at a flow rate of 1.2 mL/min after all perturbations and combinations (**Figure 5**).

**Table 3** contains the design summary for optimization, and **Table 4** provides the obtained solution for the optimised formulation.

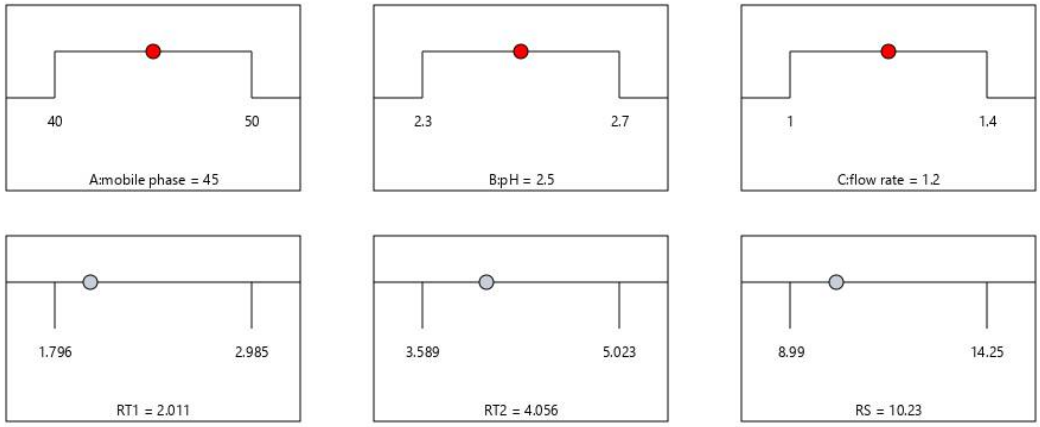



**Figure 5.** Solutions for optimised run

**Table 3.**Design summary for optimization

| Study type | Design type | Design model | Total runs |
|---|---|---|---|
| Response surface | Box-Behnken | Quadratic | 17 |

**Table 4.**Obtained solution for optimized formulation

| Runs | Factor 1 A: mobile phase | Factor 2 B: pH | Factor 3 C: flow rate | Response 1 (RT1) | Response 2 (RT2) | Response 3 (Rs) |
|---|---|---|---|---|---|---|
| 1 | 45 | 2.5 | 1.2 | 2.011 | 4.056 | 10.23 |

### Statistical Analysis of Experimental Data by Design-expert Software

The significance of the design model for the three responses was examined using analysis of variance (ANOVA), and all three responses have p-values less than 0.05, making them all significant. To see how different variables and their interactions affected the responses of the Design Expert® software, 2D contour and 3D surface plots were investigated. Dark blue and dark red sections indicate lower values and higher values, respectively. The areas with light blue, green, and yellow shading stand for middle values. According to the aforementioned 2D Contour and 3D Surface plots of RT1, RT2, and resolution (Figures 6, 7, and 8), the value of RT and resolution decreases with increasing flow rate, pH, and organic phase composition.

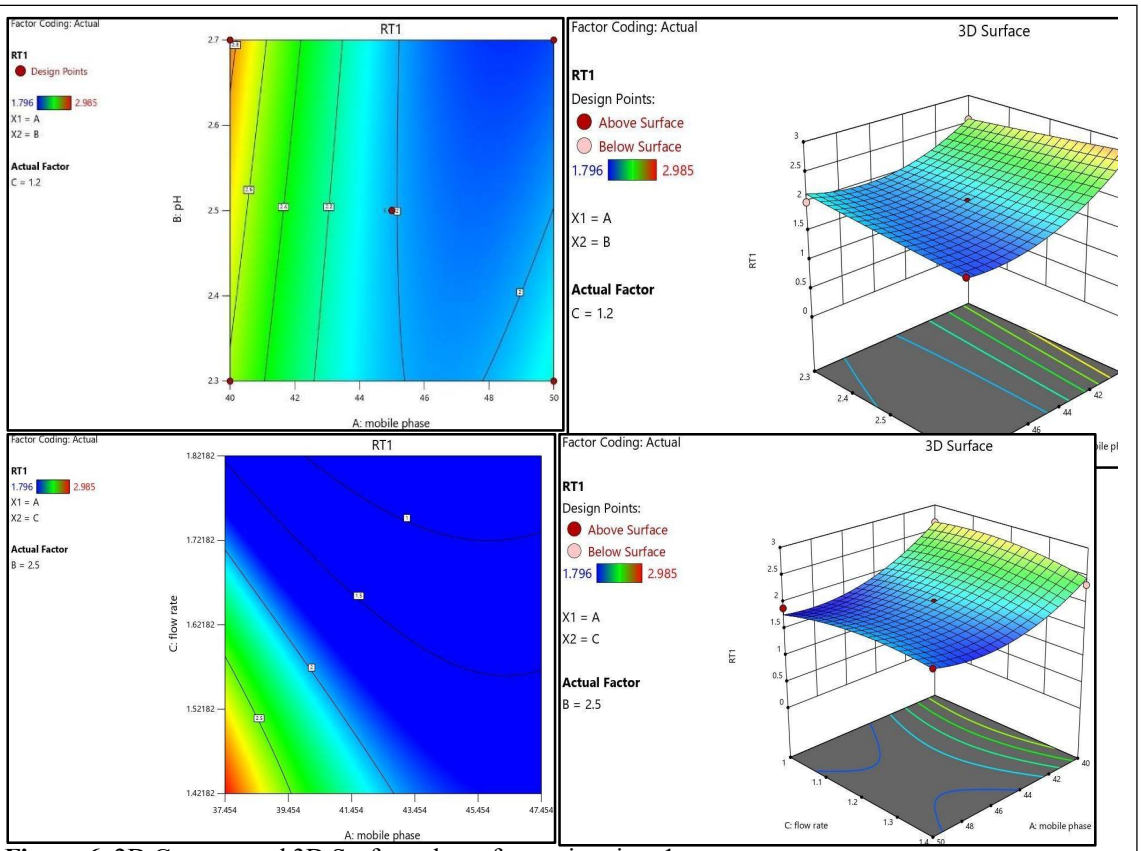



**Figure 6.** 2D Contour and 3D Surface plots of retention time 1

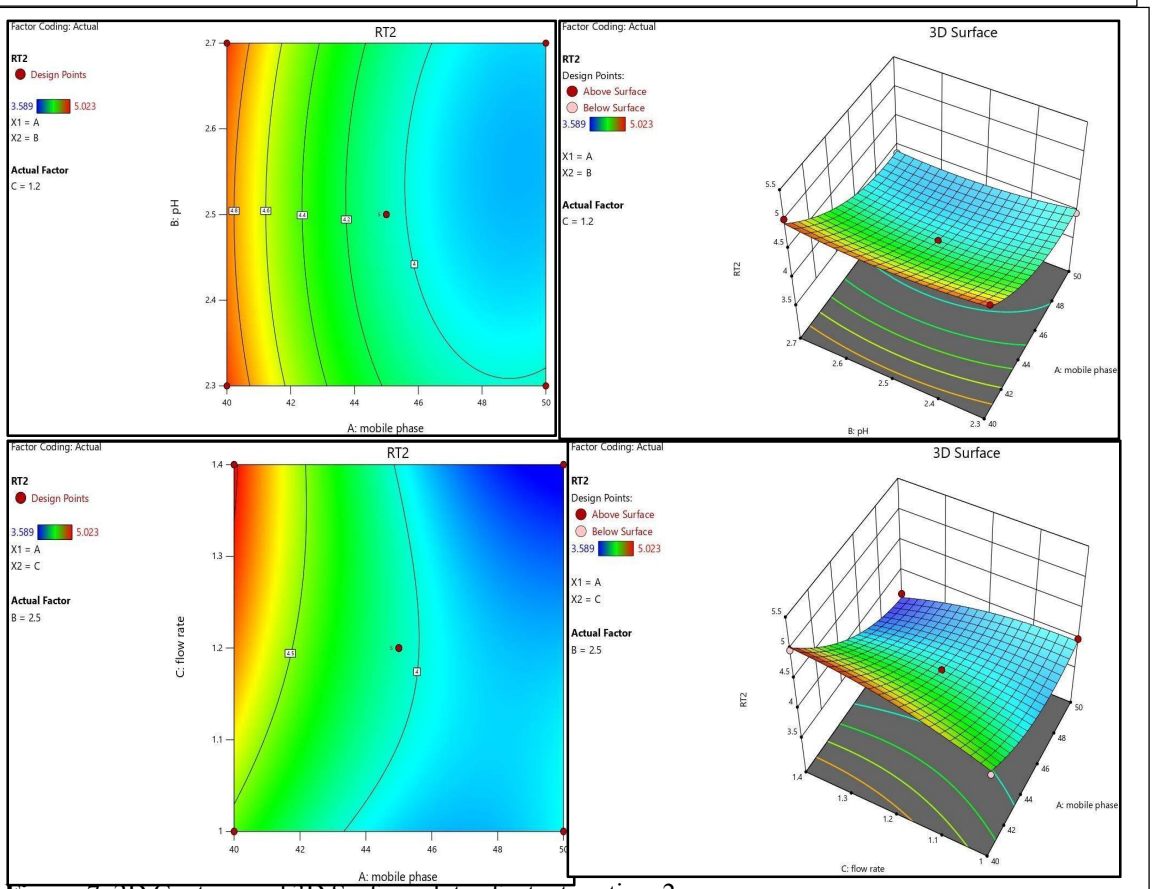



**Figure 7.** 2D Contour and 3D Surface plots of retention time 2

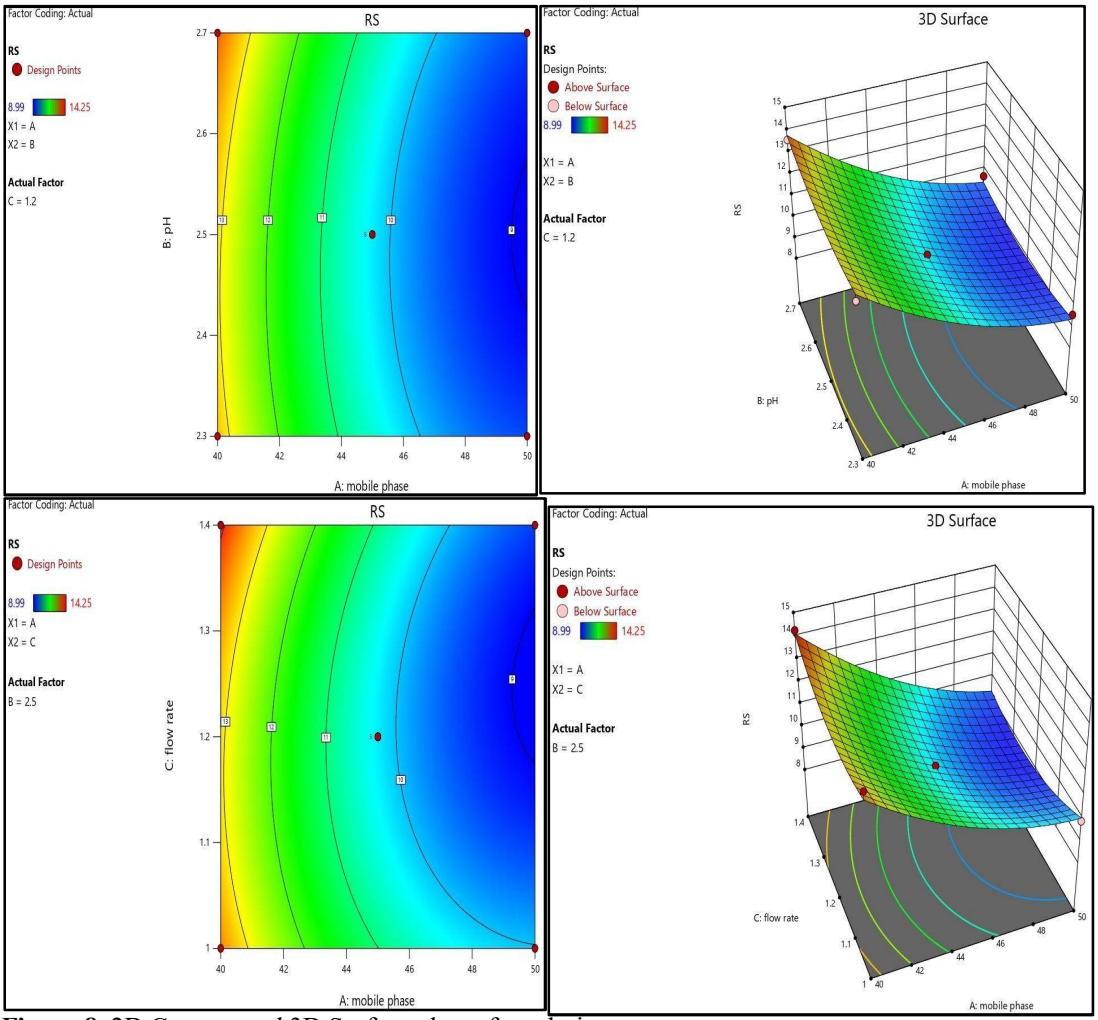



**Figure 8.** 2D Contour and 3D Surface plots of resolution

## Design Validation

The selected models for the three responses were found to be appropriate for the design specifications based on the actual versus anticipated plots for each response (Figure 9), which showed a uniform distribution of the data points around a 45$^{o}$ line. The ANOVA further demonstrated that the selected models were significant with $p < 0.05$. Consequently, the models selected were appropriate for the design used in this work.

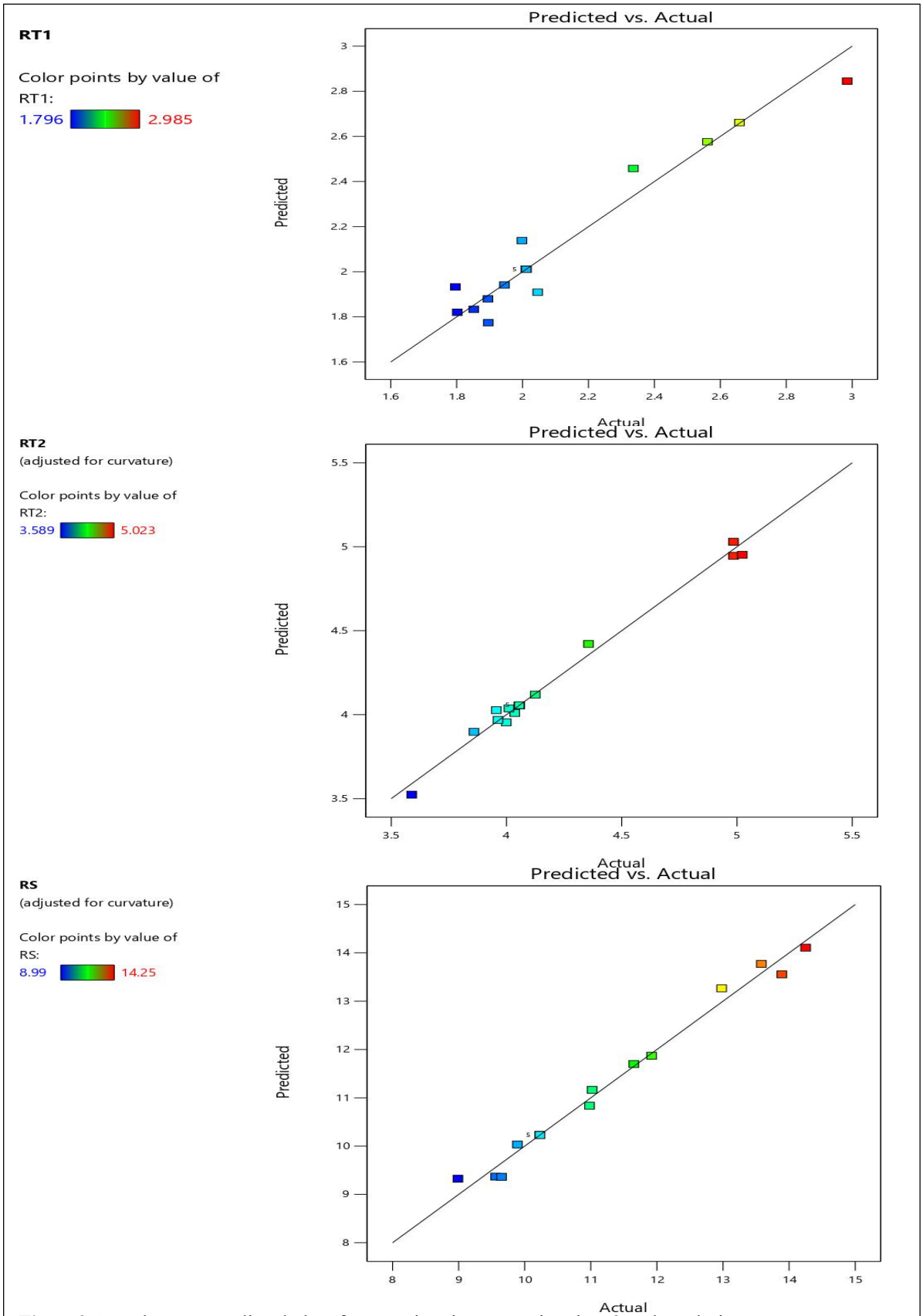



**Figure9.**Actual versus predicted plots for retention time, retention time 2 and resolution

**Overlay Plot**

The QbD design space where the method satisfies the mean performance goals and robustness criteria is illustrated by the overlay contour plot. The flag depicts the three independent parameters that were chosen optimally, giving the desired values of minimum RT, maximum theoretical plates, and minimal asymmetry (**Figure 10**).

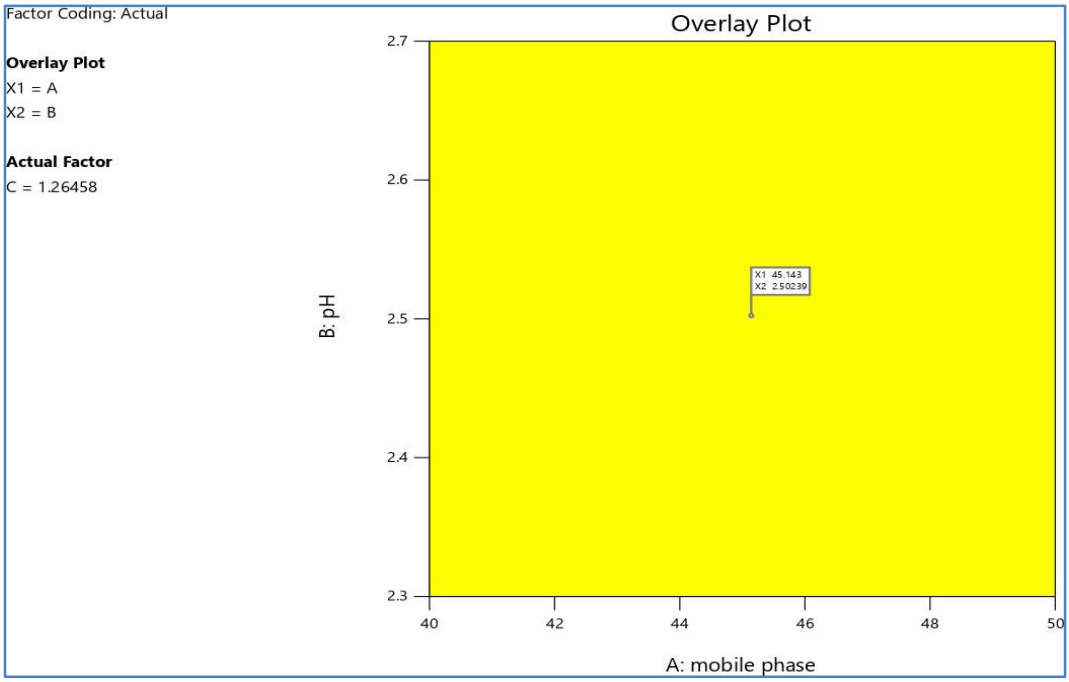



**Figure10.**Overlay plot for design space

**Method Validation**

**System suitability**

Following table (Table 5) describes the system suitability study test results. Every chromatogram in Figure 11 demonstrated system suitability parameters for study.

**Table 5.**Analytical data for System suitability

| **Parameters** | **Results** | | **Recommendations** |
|---|---|---|---|
| | **Telmisartan** | **Chlorthalidone** | |
| Theoretical plates (N) | 6020.98 | 11738.11 | Mean (n=6) > 2000 |
| Resolution (Rs) | - | 10.23 | > 2 between TEL and CHLOR |
| Tailing factor (TF) | 1.216 | 1.122 | Mean (n=6) ≤ 2 |
| Repeatability | 1.33 | 0.84 | % RSD (n=6) < 2 |

Accuracy (Percent recovery)

Percent Recovery was observed within limit (98-102%) at all three levels. Result and statistical data of accuracy for TEL and CHLOR are shown in **Table 6 and 7.**

**Table 6.**Analytical data for Accuracy of Telmisartan

| **Level (%)** | **Area** | **Added Conc.** | **Recovered Conc.** | **Mean % Recovery** | **Acceptance Criteria** | **Conclusion** |
|---|---|---|---|---|---|---|
| 80 | 740025 | 72.00 | 71.94 | 98.04 | **% Recovery 98 to 102 %** | **% Recovery was found well.** |
| | 725500 | 72.00 | 70.47 | | | |
| | 714586 | 72.00 | 69.36 | | | |
| 100 | 820256 | 80.00 | 80.05 | 99.97 | | |
| | 802564 | 80.00 | 78.26 | | | |
| | 835649 | 80.00 | 81.61 | | | |
| 120 | 914568 | 88.00 | 89.60 | 101.36 | | |
| | 902568 | 88.00 | 88.38 | | | |
| | 914568 | 88.00 | 89.60 | | | |

**Table 7.**Analytical data for Accuracy of Chlorthalidone

| Level (%) | Area | Added Conc. | Recovered Conc. | Mean % Recovery | Acceptance Criteria | Conclusion |
|---|---|---|---|---|---|---|
| 80 | 165288 | 22.5 | 21.81 | 99.25 | % Recovery 98 to 102 % | % Recovery was found well. |
| | 174689 | 22.5 | 23.27 | | | |
| | 165894 | 22.5 | 21.91 | | | |
| 100 | 195684 | 25 | 26.52 | 100.25 | | |
| | 184569 | 25 | 24.80 | | | |
| | 178546 | 25 | 23.86 | | | |
| 120 | 201548 | 27.5 | 27.42 | 101.41 | | |
| | 215468 | 27.5 | 29.58 | | | |
| | 196548 | 27.5 | 26.65 | | | |

**Precision**

The % RSD for both drug was found to be less than 2, therefore the proposed method is called as precise. Analytical data of both precision of TEL and CHLOR is given in **Table 8 and 9.**

**Table 8.** Analytical data of Precision for Telmisartan

| Precision | Mean value of 6 injections of TEL | |
|---|---|---|
| | RT | Peak area |
| Intra-day precision | 4.011 | 523449 |
| Inter-day precision | 4.043 | 508657 |
| % RSD | 1.33 | 0.98 |

**Table 9.**Analytical data of Precision for Chlorthalidone

| Precision | Mean value of 6 injections of CHLOR | |
|---|---|---|
| | RT | Peak area |
| Intra-day precision | 2.004 | |
| Inter-day precision | 2.019 | 368182 |
| % RSD | 0.84 | 1.29 |

**Linearity**

From the calibration curve, it was concluded that TEL and CHLOR shows linear response in the range of 10-50 µg/ml and 10-50 µg/ml. the correlation coefficient was found within limit. The result of data of TEL and CHLOR are given in **Table 10 and 11.** Linearity graph of both drug is depicted in (**Figure 12, 13)**

**Table 10.**Analytical data of Linearity of Telmisartan

| Conc.(µg/mL) | Area |
|---|---|
| 10 | 225654 |
| 20 | 325648 |
| 30 | 425689 |
| 40 | 524659 |
| 50 | 620255 |
| **Partition Coefficient** | 0.999 |
| **Slope** | 9882.1 |

**Table 11.**Analytical data of Linearity of Chlorthalidone

| Conc.(µg/mL) | Area |
|---|---|
| 10 | 154569 |
| 20 | 215469 |
| 30 | 285649 |
| 40 | 345689 |
| 50 | 412564 |
| **Partition Coefficient** | 0.999 |
| **Slope** | 6462.1 |

**Figure 11.**Analytical data for linearityTelmisartan

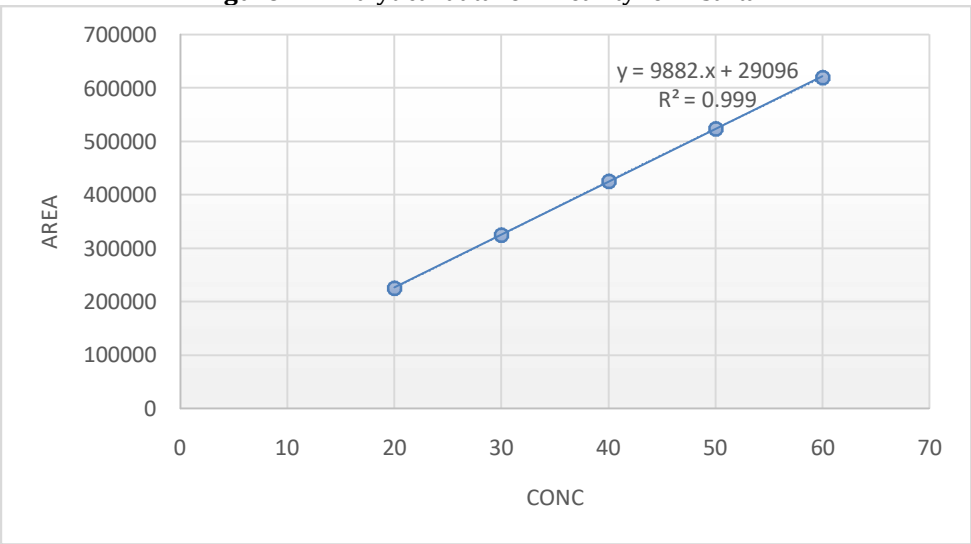
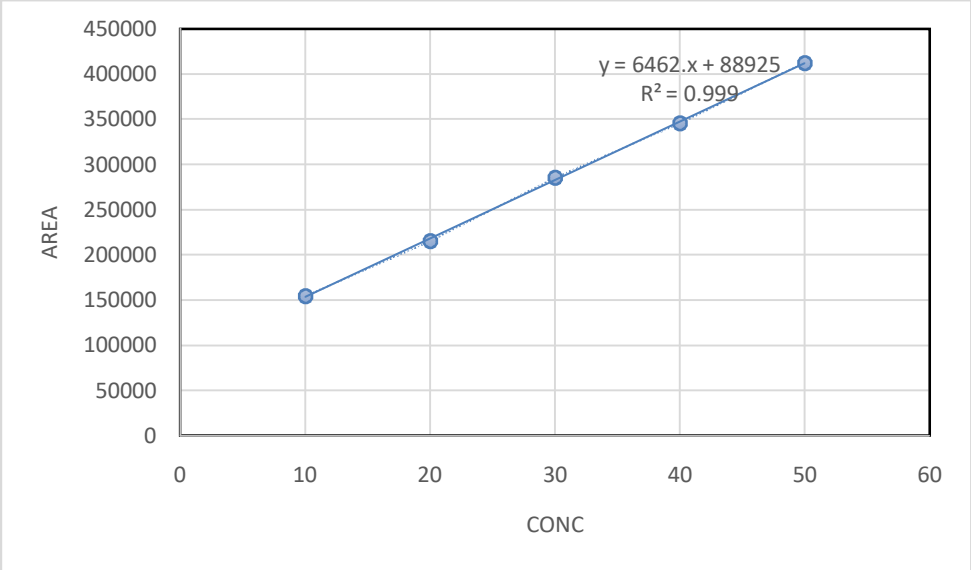



**Figure12.** Analytical data for linearityChlorthalidone




**Detection:** The result of detection limit for TEL and CHLOR is given in **Table 12.**

**Table 12**. Result of detection limit

| Parameter | TEL | CHLOR |
|---|---|---|
| LOD (µg/mL) | 1.82 | 1.88 |
| LOQ (µg/mL) | 5.41 | 5.72 |

## CONCLUSION

The purpose of this project was to use the Quality by Design (QbD) method to develop a simple, reliable, accurate, and suitable RP-HPLC system. The DOE findings for each component were analysed, including ANOVA, diagnostic graphs, and model graphs. The influence of each component on the response result was investigated in this result.

The results of all system suitability parameters were appropriate within the limitations set by adopting ICH (Q2 R1) guidelines in terms of the development and validation of analytical methods, showing that the system is operating properly and capable of providing precise and accurate results. The analysis results of the established method were validated for linearity, accuracy, precision, robustness, and detection and quantification limits.

Since the established approach is stable, reproducible, and quick, it can be used for routine research in the pharmaceutical industry on the bulk drugs TEL and CHLOR as well as the type of pharmaceutical dosage. This recently created approach for predicting TEL and CHLOR was shown to be simple, precise, and accurate, based on the experimental outcomes. It also has a shorter retention time, which improves

acceptability and lowers costs. It is suitable for routine analysis at research institutes, quality control divisions in industries, and authorised testing labs.

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**AUTHORS CONTRIBUTION:**PT and OK has done research under the guidance of ASJ. DRM and MRD has analysed the result and drafted a manuscript. ASJ and DRM has revised and finalize the manuscript.

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**DATA AVAILABILITY:** None

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