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# QBD APPROCH BASED DEVELOPMENT OF VALIDATED ANALYTICAL METHOD FOR ESTIMATION OF CLARITHROMYCIN BY RP-HPLC

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## ABSTRACT

Based on QbD, a chromatographic technique for estimation of clarithromycin from bulk was developed and validated. The method for analysis of clarithromycin is obtained by QbD trial optimization. For the QbD approach Mobile phase and flow rate are chosen as factors. While two responses were taken *i.e.*retention time and the peak area, the research was carried out using Design of Expert software. Response 1 RT outcomes are F- Value 145.44, P-Value less than 0.05, predicted & adjusted $R^2$are 0.9570 & 0.9763 respectively. Response 2 Peak Area outcomes are F- Value72.09, P-Value less than 0.05, predicted & adjusted $R^2$ are 0.8777 & 0.0.9104 respectively. The optimized batch was carried out by HPLC gradient system with auto-injector using UV (DAD) detector which had C18 quaternary gradient column at room temperature. The mobile phase was ACN: Water (09:91) with a flow rate of 0.9 ml/min. The sample was detected at a wavelength 209 nm and the sample size was 20µl. According to ICH guidelines, the purpose of method validation is to demonstrate the acceptability of an analytical technique for its intended purpose. The validated parameter includes the recovery study found (% RCVD -100), Linearity regression (0.999) which obtained a parallel calibration curve, repeatability (RSD%-0.26) and LOD & LOQ were found at 9.206µg/ml & 27.898µg/ml respectively. Acid, base, $H_2O_2$, and neutral were used in the stress degradation investigation. The degradation with acid (5.08%), base (96%), $H_2O_2$ (32.14%), and neutral (3.42%) were found. The developed approach is used to analyze clarithromycin in pharmaceutical formulations and is unique and accurate.

**Keywords:** RP-HPLC, QBD, Clarithromycin, Design of Expert.

## 1. INTRODUCTION

QBD is used to achieve enhanced method performance, high accuracy, flexibility, and robustness. The aid of analytical QBD improves the understanding and control; minimizes the instability in analytical attributes for accurate method development [1, 2]. Identifying and limiting sources of variability that may contribute to poor method robustness, as well as ensuring that the method satisfies its intended performance requirements throughout the product and method lifespan, are all advantages of applying QbD concepts to analytical techniques [3]. Clarithromycin is an antibiotic that is used to treat a number of bacterial illnesses. To treat specific forms of stomach ulcers, this medicine can be used with anti-ulcer treatments [4].This antibiotic is solely used to treat bacterial infections. It is ineffective against viral infections (such as common cold, flu) [5]. It may also be used to prevent the spread of some bacteria [6]. Clarithromycin belongs to the macrolide antibiotic family. It works by preventing bacteria from growing. When an antibiotic is used when it isn't needed, it loses its effectiveness for future illnesses. Clarithromycin is an antibiotic that is used to treat a number of bacterial illnesses. It subsequently enters the bacterial cell wall and binds reversibly to domain V of the 23S ribosomal RNA of the 50S subunit of the bacterial ribosome, preventing aminoacyl transfer-RNA and polypeptide synthesis, just like other macrolides [7]. Clarithromycin is approved for the treatment of bronchitis, treatment of ears sinuses, throat and skin, etc. Clarithromycin is converted to 14-OH clarithromycin, which is active and functions in tandem with its parent molecule [8]. To treat specific forms of stomach ulcers, this medicine can be used with anti-ulcer treatments. It may also be used to prevent the spread of

some bacteria. Clarithromycin belongs to the macrolide antibiotic family. It works by preventing bacteria from growing. This antibiotic is solely used to treat bacterial infections. It is ineffective against viral infections (such as common cold, flu). When an antibiotic is used when it isn't needed, it loses its effectiveness for future illnesses [9].

Clarithromycin was approved on 20 October 2000 by FDA [10]. The hepatic microsomal CYP3A4 isoenzyme and P-glycoprotein, an energy-dependent drug efflux pump, are likewise inhibited by clarithromycin.

The objective of this work is to develop a RP-HPLC method for assessing Clarithromycin in pharmaceutical tablet dosage forms that is easy, efficient, accurate, and proven. Validation of accuracy, precision, linearity, and resilience in accordance with ICH standards.

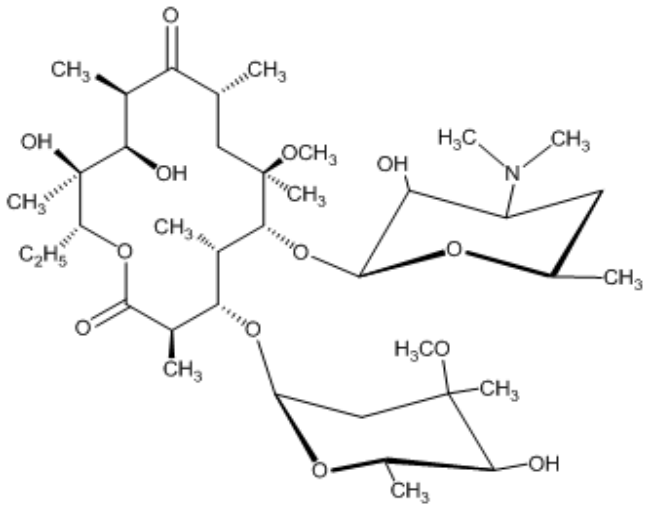

**Fig. 1: Structure of Clarithromycin**

**Table 1: Clarithromycin drug profile**

| | |
|---|---|
| Chemical name | 6-O-methylerythromycin |
| CAS ID | 81103-11-9 |
| Brand name | Biaxin and Biaxin XL |
| Class | Macrolide antibiotics |
| Mol. Formula | C38H69NO13 |
| Mol. Weight | 747.953 g/mol |
| Antimicrobial Spectrum | Mainly active against gram-positive (Staphylococcus aureus, S. pneumonia, and S. pyogenes) and gram-negative aerobic bacteria (Haemophilusinfluenzae, H. |
| Solubility | Soluble in acetone and acetonitrile, Insoluble in water (0.33 mg/l) |
| Ph value | 5.0-8.0 |
| pka value | Strong acidic- 12.46, Strong basic- 8.38 |
| Polarity | Log P 2.69 |
| Bioavailability | Oral 50% (250 mg) |
| Protein binding | 72% bound to plasma proteins at a concentration of 0·45 mg $l^{-1}$ |
| Metabolism | Hepatic (CYP involved) |
| Dose | Adult- 250-500 mg orally every 12 hours for 7-14 days<br>Pediatric- 15 mg/kg/day orally divided every 12 hours for 10 days |
| Half life | 8 to 12 hours |
| Excretion | Renal (30%-40%), bile |
| Melting point | 217-220°C |
| storage | Store at room temperature away from light and moisture |
| ʎmax | 210 nm |

## 2. EXPERIMENTAL

### 2.1. Selection of analytical wavelength

#### *2.1.1. Preparation of standard stock solution*

Methanol was used as solvent for dissolving clarithromycin. For the preparation of stock solution, 10mg of drug clarithromycin was taken into 10ml volumetric flask, 8ml of methanol was added and sonicated to dissolve the standard completely and made up to mark with methanol (1000µg). Further diluted 1ml to 10ml methanol (10µg/ml).

#### *2.1.2. Selection of analytical wavelength*

Methanol as a blank and clarithromycin standard solution (10µg) was scanned from 400nm to 200nm. Absorption maxima were determined for drug. Clarithromycin showed maximum absorbance at 209nm.

## 2.2. Method Development by RP-HPLC

### *2.2.1. Preparation of standard stock solution for Chromatographic development*

In order to prepare a standard stock solution, 10mg clarithromycin API was dissolved in 10ml of diluents (water:ACN 9:1) Analytical wavelength for the examination was selected from the wavelength of maximum absorption from the spectrophotometric analysis and it was 209nm.

### *2.2.2. Optimization of RP-HPLC Method*

Reversed-Phase Liquid Chromatography with Isocratic elution and UV detection was performed.

**Table 2: Optimized Chromatographic Conditions for Clarithromycin**

| Parameter | Description |
|---|---|
| Mode | Isogradient Auto injector |
| Column Name | Kromasil C18, 250 mm X 4.6mm ID, 5 µm |
| Detector | UV (DAD) G13148 |
| Injection Volume | 20 µl |
| Wavelength | 209 nm |
| Column Oven temp | 28°C |
| Mobile Phase | ACN:Water (1:9%V/V) |
| Flow Rate | 0.95 ml/min |
| Particle size | 4.6µm |
| Run time | 10 Minutes |
| pump | Quaternary gradient (G130A) |
| Software | Chemstation 10.1 |

### *2.2.3. Preparation of System Suitability Test (Clarithromycin Standard Solution)*

Twenty clarithromycin tablets of 500 mg each, as well as a powder containing 500 mg clarithromycin, were carefully weighed and placed in a 100 ml volumetric flask. It was observed that the equivalency weight for 10 mg is 21.78 mg. The 1000 g/ml tab solution was prepared by combining 21.78 mg powder with 10 ml methanol (1000µg concentration), and chromatograms were recorded.

System suitability is a Pharmacopoeial requirement and is used to verify, whether the chromatographic system is adequate for analysis to be done. The tests were performed by collecting data from five replicate injections of standard drug solution and the results are recorded.

Acceptance criteria

1. RSD should not be more than 2.0 % for five replicate injections of standard.
2. USP Tailing Factor/ Asymmetry Factor is not more than 2.0.
3. The column efficiency as determined for Plate Count should be more than 2000.

### *2.2.4. QbD Approach to method Development*

Advantages of applying QbD concepts to analytical techniques are identifying and limiting sources of variability that may contribute to poor method robustness, as well as ensuring that the method satisfies its intended performance requirements throughout the product and method lifespan.

For chromatogram optimization 20µg/ml solvent was used.

Mobile phase- ACN: Water (10:90); Flow Rate- 1ml/ min; Wavelength- 209nm

The obtained result was forwarded to QbD optimization and QbD supplied eight batches, which were all run and recorded.

**Table 3: Optimized method for QbD**

| Retention Time | Area | Theoretical plate | Tailing factor |
|---|---|---|---|
| 5.096 | 1561.3877 | 10604 | 0.99 |

**Table 4: QbD Batches**

| | | Factor 1 | Factor 2 | Response 1 | Response 2 | Response 3 | Response 4 |
|---|---|---|---|---|---|---|---|
| std | run | Water % | Flow rate ml/min | RT | PA | TP | TF |
| 6 | 1 | 92.5 | 0.95 | 8.414 | 2122.66 | 7234 | 0.93 |
| 3 | 2 | 90 | 1 | 6.349 | 2089.06 | 6925 | 0.93 |
| 2 | 3 | 92 | 0.9 | 8.703 | 2347.27 | 6717 | 0.93 |
| 5 | 4 | 89.5 | 0.95 | 6.471 | 2204.17 | 7194 | 0.92 |
| 7 | 5 | 91 | 0.875 | 7.843 | 2331.58 | 7825 | 0.93 |
| 4 | 6 | 92 | 1 | 7.604 | 2044.18 | 6569 | 0.94 |
| 1 | 7 | 90 | 0.9 | 7.082 | 2272.23 | 7192 | 0.92 |
| 8 | 8 | 91 | 1.025 | 6.754 | 2025.05 | 6706 | 0.94 |

### 2.3. Validation of RP-HPLC method

The developed method for estimation of Clarithromycin was validated as per ICH guidelines for the following parameters.

The following solutions were prepared and injected to prove the specificity nature of the method. (Checked peak purity for standard and test sample solution)

1. Blank (Methanol as a diluent)
2. Placebo
3. Clarithromycin Standard solution
4. Tablet test sample solution

#### *2.3.1. Linearity*

The linearity is the capacity of an analytical method to elicit check results that are proportional to the concentration of analytes in a specific range, either directly or through well-defined mathematical adjustments.

The 1000 g/ml tab solution was prepared by combining 21.78 mg powder with 10 ml methanol (1000µg concentration). Five test samples were prepared and recorded the results.

#### *2.3.2. Accuracy*

The accuracy of recovery studies is determined by combining three standard levels. Produced 80 percent, 100 percent, and 120 percent samples by mixing 0.1ml of tab solution with 8, 10, or 12g/ml of standard solution (respectively) and topping up with 10ml mobile phase for accuracy validation. The findings are presented in a recovery study format.

The % recovery should be in the range of 98%-102% and relative standard deviation not more than 2.0%. Take 10µg/ml tab solution for accuracy.

**Table 5: Results and statistical data for accuracy**

| % Level | Tab solution (ml) | Std solution (µg/ml) Concentration | Vol. make up m.p (ml) |
|---|---|---|---|
| 80% | 0.1 | 08 | 10 |
| 100% | 0.1 | 10 | 10 |
| 120% | 0.1 | 12 | 10 |

#### *2.3.3. Precision*

Twenty tablets were weighed and crushed into a fine powder. The powder material weighing equivalent to 10 mg of clarithromycin was precisely weighed and put into a 10 ml volumetric flask with 7 ml methanol added, sonicated for 15 minutes with intermittent shaking. After mixing the solution, made up the volume with methanol up to the mark (1000µg/ml), injected the resultant solution and chromatograms were recorded and results were recorded.

For acceptance % assay should be 98% to 102% and % RSD not more than 2.0%

#### *2.3.4. Robustness study*

Blank and Standard solution were injected under different chromatographic conditions. The recorded changes should be minor for acceptance the method.

**Table 6: Statistical data for Robustness**

| Changed parameters | QbDOptimized values | Changed values |
|---|---|---|
| Flow rate (ml/min) | 0.9 | 0.85<br>1.05 |
| Mobile phase | 91:09 | 90:10<br>92:08 |
| Wavelength (nm) | 209 | 208<br>210 |

### 2.4. Forced degradation

The degradation study performed under various physical lab conditions and lab chemical mixture. 10µg test sample was used for degradation study.

**Table 7: Data for Degradation sample preparation**

| Lab mixture | Mixture QTY (ml) | Sample taken from stock (API)10µg (ml) | Time (mins) |
|---|---|---|---|
| 0.1 N NaOH | 5 | 0.1 | 60-120 |
| 1.1 N HCl | 5 | 0.1 | 60-120 |
| 3% $H_2O_2$ | 5 | 0.1 | 60-120 |
| Neutral | 5 | 0.1 | 60-120 |

### 2.5. Chemical degradation

#### *2.5.1. Acid degradation*

Forced degradation was performed for both physical lab mixture of tablet and placebo under acidic condition. 5 N HCl (42.5 ml of HCl diluted to 100 ml with water) was prepared for this study.

#### *2.5.2. Base/Alkaline degradation*

Forced degradation was performed for both physical lab mixture of tablet and placebo under alkaline condition. 5 N NaOH (20 gm of NaOH dissolved in 100 ml of water) was prepared for study.

#### *2.5.3. Peroxide degradation*

Forced degradation was performed for physical lab mixture of tablet. 30% hydrogen peroxide solution and 30% sodium sulfite solution was used for study.

## 3. RESULTS AND DISCUSSION

### 3.1. Selection of analytical wavelength

The analytical wavelength is determined by UV Spectroscopy. The 10µg clarithromycin in methanol sample was prepared and ʎmax was observed.

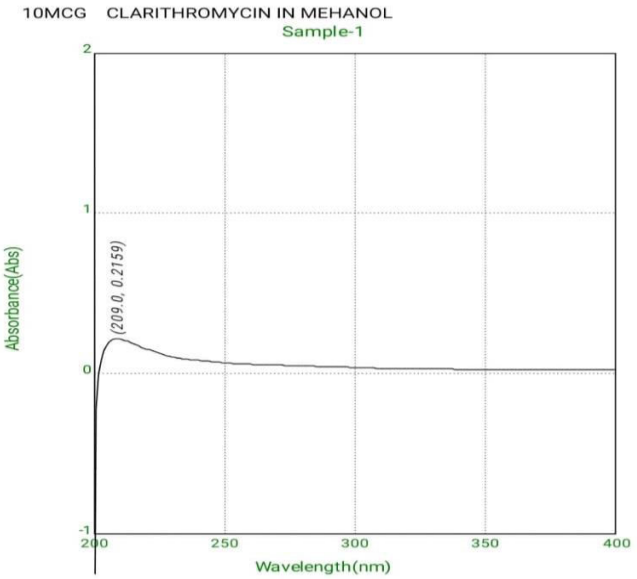


**Fig. 2: UV-Vis spectral of clarithromycin in methanol**

### 3.2. Optimization of RP-HPLC Method by QbD

The chromatographic settings in this experiment were found to yield a better peak, good retention time, and tailing factor, hence they were chosen for method validation.

#### *3.2.1. ANOVA for Linear model*

**Response 1: Retention Time**

Factor coding is **Coded**;Sum of squares is Type III-Partial**. The** Model F-value of 145.44 implies the model is significant. There is only a 0.01% chance that an F-value this large could occur due to noise. P-values less than 0.0500 indicate model terms are significant. In this case A, B are significant model terms. Values greater than 0.1000 indicate the model terms are not significant. If there are many insignificant model terms (not counting those required to support hierarchy), model reduction may improve your model.

The Predicted $R^2$ of 0.9570 is in reasonable agreement with the Adjusted $R^2$ of 0.9763; i.e. the difference is less than 0.2.Adeq Precision measures the signal to noise ratio. A ratio greater than 4 is desirable. Your ratio of 26.203 indicates an adequate signal. This model can be used to navigate the design space.

The coefficient estimate represents the expected change in response per unit change in factor value when all remaining factors are held constant. The intercept in an orthogonal design is the overall average response of all the runs. The coefficients are adjustments around that average based on the factor settings. When the factors are orthogonal, the VIFs are 1; VIFs greater than 1 indicate multi-colinearity, the higher the VIF, the more severe the correlation of factors. As a rough rule, VIFs less than 10 are tolerable.

**Table 8: Model of P and F Value**

| Source | Sum of Squares | df | Mean Square | F-value | p-value | |
|---|---|---|---|---|---|---|
| **Model** | 5.37 | 2 | 2.68 | 145.44 | < 0.0001 | significant |
| A-ACN | 3.95 | 1 | 3.95 | 214.29 | < 0.0001 | |
| B-Flow rate | 1.41 | 1 | 1.41 | 76.60 | 0.0003 | |
| **Residual** | 0.0922 | 5 | 0.0184 | | | |
| **Cor Total** | 5.46 | 7 | | | | |

**Table 9: Fit Statistics**

| | | | |
|---|---|---|---|
| **Std. Dev.** | 0.1358 | **$R^2$** | 0.9831 |
| **Mean** | 7.40 | **Adjusted $R^2$** | 0.9763 |
| **C.V. %** | 1.83 | **Predicted $R^2$** | 0.9570 |
| | | **Adeq Precision** | 26.2027 |

**Table 10: Coefficients in Terms of Coded Factors**

| Factor | Coefficient Estimate | df | Standard Error | 95% CI Low | 95% CI High | VIF |
|---|---|---|---|---|---|---|
| Intercept | 7.40 | 1 | 0.0480 | 7.28 | 7.53 | |
| A-ACN | 0.6819 | 1 | 0.0466 | 0.5622 | 0.8017 | 1.0000 |
| B-Flow rate | -0.4077 | 1 | 0.0466 | -0.5275 | -0.2880 | 1.0000 |

### *3.2.2. ANOVA for Reduced Linear model*

**Response 2: Peak Area**

Factor coding is Coded; Sum of squares is Type III - Partial. The Model F-value of 72.09 implies the model is significant. There is only a 0.01% chance that an F-value this large could occur due to noise.

P-values less than 0.0500 indicate model terms are significant. In this case B is a significant model term. Values greater than 0.1000 indicate the model terms are not significant. If there are many insignificant model terms (not counting those required to support hierarchy), model reduction may improve your model.

The Predicted $R^2$ of 0.8777 is in reasonable agreement with the Adjusted $R^2$ of 0.9104; *i.e.* the difference is less than 0.2.Adeq Precision measures the signal to noise ratio. A ratio greater than 4 is desirable. Ratio of 17.474 indicates an adequate signal. This model can be used to navigate the design space.

The coefficient estimate represents the expected change in response per unit change in factor value when all remaining factors are held constant. The intercept in an orthogonal design is the overall average response of all the runs. The coefficients are adjustments around that average based on the factor settings. When the factors are orthogonal the VIFs are 1; VIFs greater than 1 indicate multi-colinearity, the higher the VIF the more severe the correlation of factors. As a rough rule, VIFs less than 10 are tolerable.

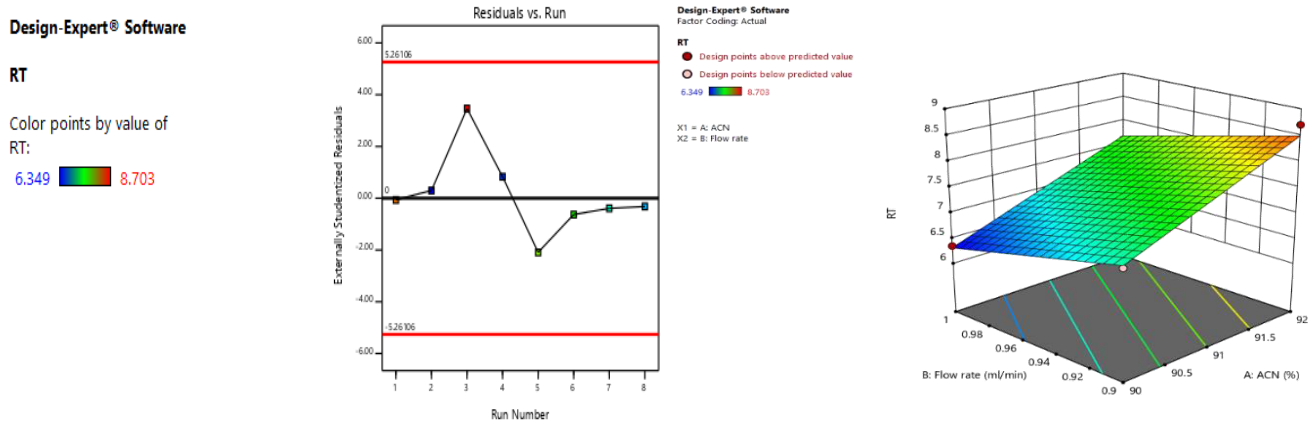


**Fig. 3: DOE for RT Response**

**Table 11: Model of P and F Value**

| Source | Sum of Squares | df | Mean Square | F-value | p-value | |
|---|---|---|---|---|---|---|
| **Model** | 1.053E+05 | 1 | 1.053E+05 | 72.09 | 0.0001 | significant |
| B-Flow rate | 1.053E+05 | 1 | 1.053E+05 | 72.09 | 0.0001 | |
| **Residual** | 8763.06 | 6 | 1460.51 | | | |
| **Cor Total** | 1.141E+05 | 7 | | | | |

**Table 12: Fit Statistics**

| | | | |
|---|---|---|---|
| **Std. Dev.** | 38.22 | **$R^2$** | 0.9232 |
| **Mean** | 2179.53 | **Adjusted $R^2$** | 0.9104 |
| **C.V. %** | 1.75 | **Predicted $R^2$** | 0.8777 |
| | | **Adeq Precision** | 17.4739 |

**Table 13: Coefficients in Terms of Coded Factors**

| Factor | Coefficient Estimate | df | Standard Error | 95% CI Low | 95% CI High | VIF |
|---|---|---|---|---|---|---|
| Intercept | 2179.53 | 1 | 13.51 | 2146.47 | 2212.59 | |
| B-Flow rate | -111.30 | 1 | 13.11 | -143.37 | -79.22 | 1.0000 |

**Table 14: CCD Optimized design batch**

| Name | Unit | Low | High | -alpha | +alpha |
|---|---|---|---|---|---|
| Water | % | 90 | 92 | 89.5 | 92.5 |
| Flow rate | ml/min | 0.9 | 1 | 0.875 | 1.025 |

Twenty tablets containing 500 mg clarithromycin were carefully weighed and placed in a 100 ml volumetric flask, as was powder comprising 500 mg clarithromycin. The equivalence weight for 10 mg was discovered to be 21.78 mg. The 1000 µg/ml tab solution was made by dissolving 21.78mg powder in 10 ml methanol. For the test, 20µg/ml was used.

### 3.3. Validation of RP-HPLC method

#### *3.3.1. Specificity*

Peak purity for Standard as well as test solution was well within limits. Hence, developed chromatographic method passed the criteria for specificity.

#### *3.3.2. Linearity*

The respective linear equation for Clarithromycin was

Y = 44.0538x + 17.1043

Where, x isconcentration of Analyte in µg/mL, y is area of peak, M isSlope and CisIntercept

There were 3 concentrations prepared 80%, 100% & 120% respectively for accuracy study. The results are shown in the table 17.

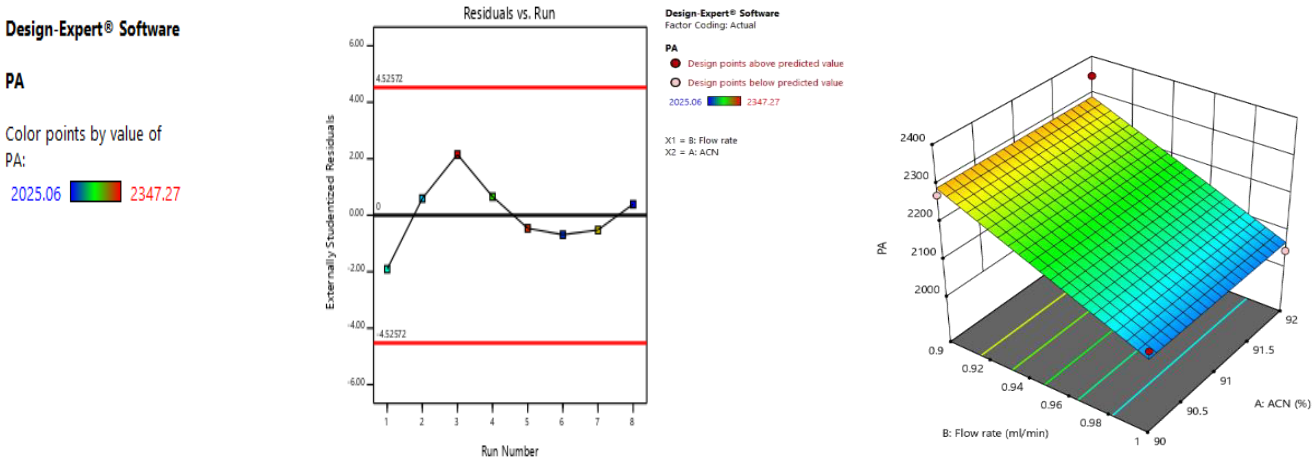


**Fig. 4: DOE for RT**

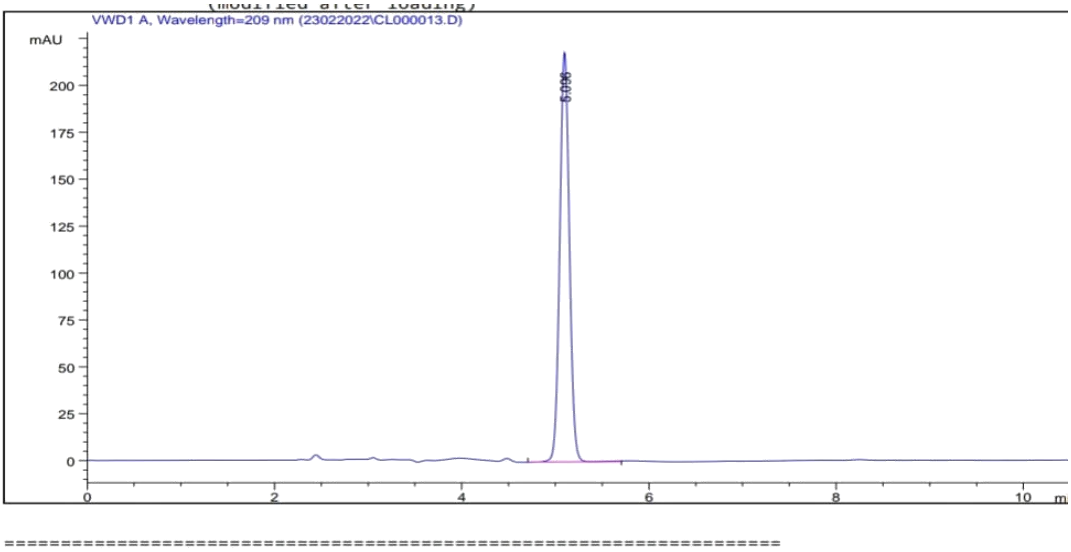


**Fig. 5: Chromatogram of QbD optimized Batch**

**Table 15: Specificity results**

| Description | Observation |
|---|---|
| Blank | No interference at R.T. of Clarithromycin due to blank |
| Placebo | No interference at R.T. of Clarithromycin due to placebo |

**Table 16: Linearity results**

| Sr no. | Parameter | Result value | Acceptance criteria |
|---|---|---|---|
| 1 | Beer's linearity range | 10-60 µg/ml | NA |
| 2 | Correlation coefficient ($R^2$) | 0.99999 | NLT 0.98 |
| 3 | Intercept | 17.1 c | To be report |
| 4 | Slope | 44.05m | To be report |
| 5 | % RSD for area at each level | 0.21 | NMT 2.0 |

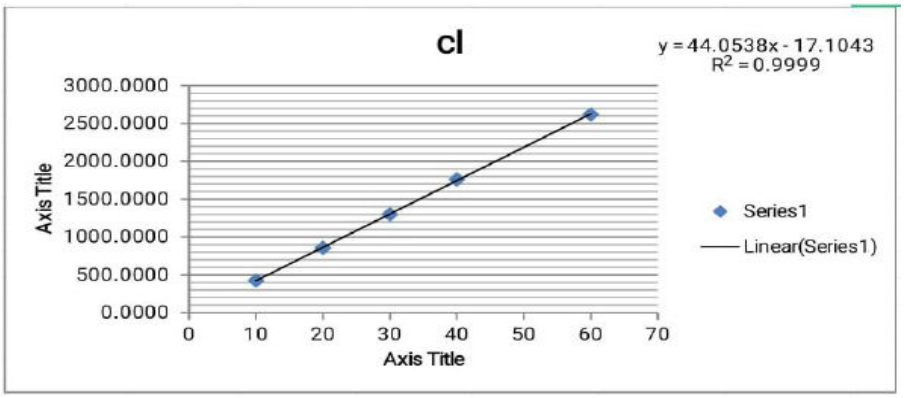


**Fig. 6: Calibration curve for clarithromycin**

**Table 17: Accuracy Results**

| Concentration (%) | Amount added | Amount recovered | % Recovery |
|---|---|---|---|
| 80 | 8 | 7.96 | 99.49 |
| | 8 | 8.01 | 100.09 |
| 100 | 10 | 10.04 | 100.48 |
| | 10 | 10.13 | 101.00 |
| 120 | 12 | 12.06 | 100.72 |
| | 12 | 12.04 | 10048 |

*% Recovery = 100.37%, Acceptance Criteria 98%- 102%*

**Table 18: Precision Results**

| Concentration | Area | %Amount found | %RSD |
|---|---|---|---|
| 20 | 895.16 | 99.67 | 0.25 |
| 40 | 1314.07 | 98.14 | 0.54 |
| 60 | 1780.74 | 100.13 | 0.12 |

*Acceptance Criteria: Assay Value= 90-110%, % RSD=not more than 2*

**Table 19: Repeatability Results**

| Concentration | Area | %Amount found | %RSD |
|---|---|---|---|
| 30 | 1310.11 | 98.03 | 0.26 |

**Table 20: Robustness Results**

| Parameters | Changed value | Area | SD | %RSD |
|---|---|---|---|---|
| Flow rate (ml) | 0.85 | 1418.82 | 1.06 | 0.07 |
| | 1.05 | 1201.76 | 2.52 | 0.21 |
| Mobile phase | 90:10 | 1262.06 | 0.597 | 0.05 |
| | 92:08 | 1274.36 | 2.76 | 0.22 |
| Wavelength (nm) | 208 | 1349.36 | 4.43 | 0.33 |
| | 210 | 1188.63 | 1.12 | 0.09 |

### *3.3.3. Limit of Detection (LOD) and Limit of Quantitation (LOQ):*

Standard deviation (σ) = 2.7898, S = 44.05 (Slope)

**Detection limit (LOD):**

LOD = 3.3 σ / S

LOD = 3.3 x 2.7898 / 44.05

**LOD = 0.208989 µg/mL**

**Quantitation limit (LOQ):**

LOQ = 10 σ / S

LOQ = 10 x 2.7898 / 44.05

**LOQ = 0.63333 µg/mL**

### 3.4. Stress Degradation study

**Table 21: Forced Degradation Results**

| Degradation | Area of degrades sample | Degrade up to % | Actual % Degradation |
|---|---|---|---|
| Acid | 425.99 | 94.12 | 5.88 |
| Base | 425.99 | 3.62 | 96.38 |
| H2H2 | 425.99 | 67.86 | 32.14 |
| Neutral | 425.99 | 95.58 | 3.42 |

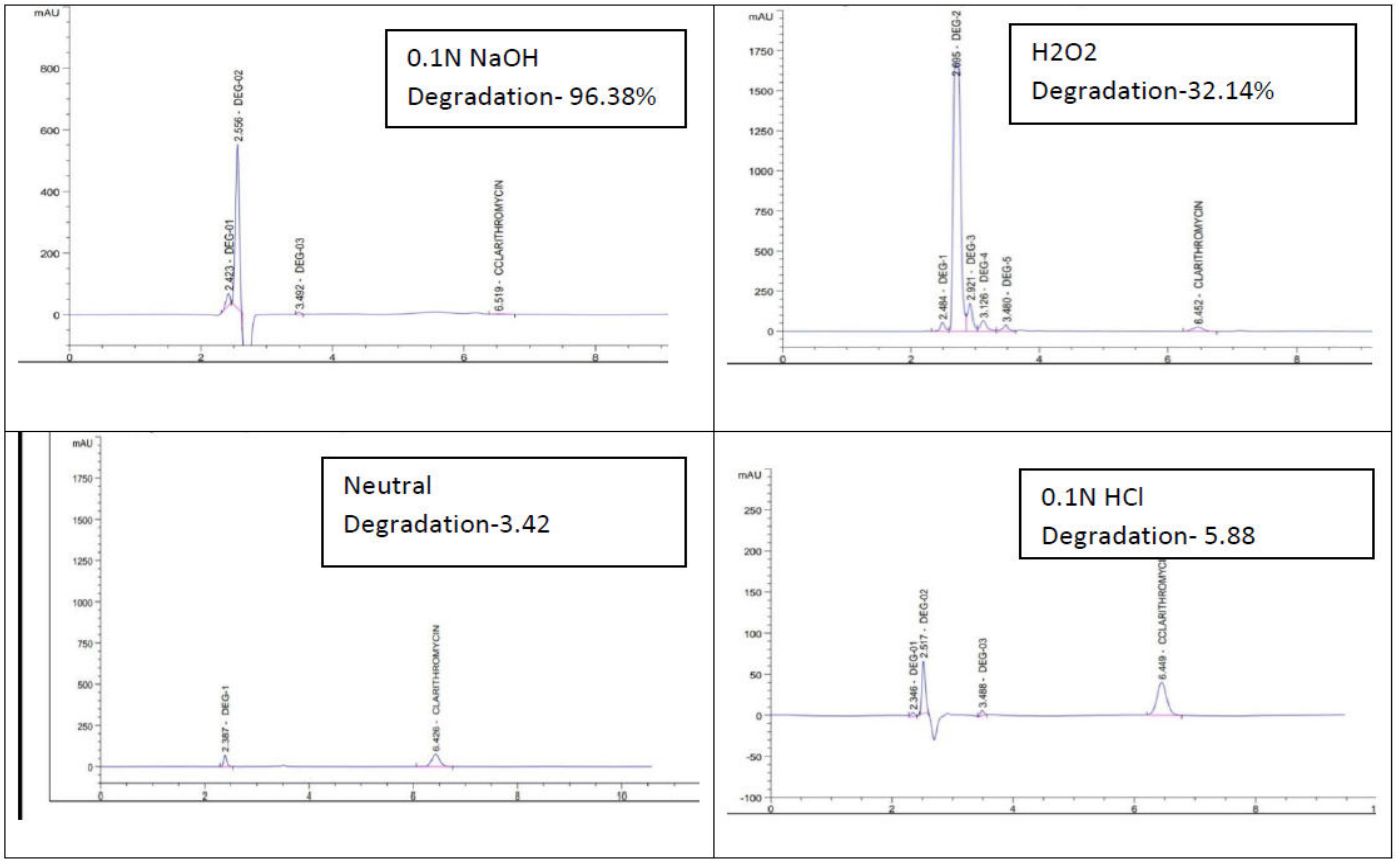


**Fig. 7: Chromatograms of analytes with chemical lab mixtures**

## 4. CONCLUSION

The QbD-based developed method by RP-HPLC is used to analysis of clarithromycin in bulk or various pharmaceutical preparations. The approach created was exact, repeatable, precise, and particular. The approach is also used to test product stability and quality in a variety of physical lab combinations. This method used in routine analysis and quality control of clarithromycin.

## 5. ACKNOWLEGMENT

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### *Conflicts of interest*

None declared

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