# QUALITY BY DESIGN DRIVEN ANALYTICAL METHOD VALIDATION

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**Abstract.** Introduction of efficient chromatographic and modified spectral techniques has revolutionized analytical method development. There is a rapid and continuous growth in the field of pharmaceutical analysis which has expedited solving the complex analytical problems with improved sensitivity and selectivity in estimation. Analytical method development and validation is an integral part of drug and formulation development and remains vital throughout its lifetime. Analytical methods are developed as quality indicating parameter for new molecules, formulations, process, residues analysis, degradation studies and impurity profiling. This review focuses on understanding and implementing the validation guidelines for analytical methods. Evidently, the concept of quality by design has paved its way in the last decade for in-depth understanding of the method. Moreover, it helps in the development of a robust method and thereby boost confidence in estimation. The current review article discusses various analytical method validation parameters, the way to perform those studies, acceptance criteria for each parameter and the importance and implementation of quality by design in analytical method development and validation and gives insight about the recent publication trends in this regard. From the publication trend of a decade, a significant rise in the analytical method development based on quality based design was observed.
**Keywords**: *validation, specificity, precision, linearity, LOQ and LOD, QbD*

## Introduction

Validation is the systematic series of operations to confirm that the analytical method, system, or equipment is appropriate for its desired use (Food and Drug Administration, 2000). Before introducing the analytical method in routine analysis, it should be validated or revalidated upon alteration in method parameters. Quality by design (QbD) is found important in analytical method development and validation for obtaining a robust method by identifying allowed space and flexibility in a given design. It also gives in-depth knowledge about the analytical method through identification of Analytical Target Profile (ATP), Critical Quality Attributes (CQA), risk assessment, Design Space (DS), Control Strategy (CS), lifecycle management and continual improvement. To develop the liquid chromatographic method using a trial and error approach, one should vary a single method parameter at a time and examine its effect on the resolution and other performance parameters, which makes this approach time-consuming. On the contrary, by QbD approach, all factors that affect method performance can be studied simultaneously which reduces the time and number of experiments while developing and validating analytical method (Hubert et al., 2014). QbD can be more efficiently implemented through different experimental design

software like Minitab by minitab limited, JMP by SAS, SPPS by IBM, Statistica by statsoft, Design expert by State ease, MODDE by Umetrics, Unscrambler, Reliasoftweibull++ by HBM prenscia. Validation parameters as per USP are given below (Chapter, 2007) and are arranged in the order of optimum sequence in which it should be executed: (1) Specificity; (2) Precision (retention time and peak area); (3) Linearity and range; (4) LOQ (quantitative limit); (5) LOD; (6) Trueness/accuracy, at different concentrations; and (7) Robustness.

### *Selectivity-specificity*

If method responds to only an analyte accurately and precisely, it is called specific and if a method responds to other chemical also it is said to be selective (accurately measures analyte in presence of interference). ICH defines specificity as the ability to assess unequivocally the analyte in the presence of components that may be expected to be present, such as impurities, degradation products, and matrix components (ICH, 2005). Lack of specificity of an individual analytical procedure may be compensated by other supporting analytical procedures.

### *Demonstration of selectivity*

It can be verified by following ways (Papadoyannis and Samanidou, 2004): (1) Absence of response in the blank/matrix, intercept of the calibration curve close to zero; and (2) Peak purity to assess if the response is owing to a single entity only.

### *Precision*

It is degree of agreement between individual test results. The results may not necessarily be correct or expected (Ferenczi-Fodor et al., 2010). *Table 1* elaborates various precision parameters. RSD of peak area or peak height or response should be NMT 2%. There should not be any variation in the same lab/

***Table 1.*** *Precision parameters.*

| Parameter | Procedure |
|---|---|
| System repeatability | 6 injection of the identical standard solution. (100 % of test concentration). |
| Method repeatability/ Intra-assay precision. (sample preparation should start by independent weighing done on short interval). | At least 5 to 6 determinations of three different matrices at 3 concentrations. (Upper, lower and middle concentration).<br>6 independent solution preparation and injection of the standard or 6 determinations at 100 % of the test concentration.<br>A minimum of 9 determinations covering the specified range for the procedure (e.g.3 concentrations/3 replicate each). |
| Intermediate precision.(Ruggedness) Determines long term variability of measurement process in the same laboratory. | One or more variation may be done-different operators, different instruments, standards and reagent from different suppliers, columns from different batches, analysis performed on separate days. |
| Reproducibility/inter-laboratory tests. It is the precision obtained between laboratories. | Analyze aliquots from homogeneous lots in different laboratories with different analysts and by using operational and environmental conditions that may differ from, but are still within the specified, parameters of method. |
| Intraday precision and Interday precision | It is often expressed relative to one day as intra-day (within-day) or relative to a period of days, as interday (between days) precision. |

### *Linearity and range*

It is ability to extract test results which are directly or by mathematical transformation are proportional to the concentration of analytes in samples within a given range (Rozet et al., 2007): (1) Concentration range spans 80-120% of expected

concentration; (2) Such three to six injections of five or more standards should be made; and (3) The regression value obtained should be less than 1.

***Approaches to prove linearity of method***

(1) Residuals: Plot deviations from the regression line versus concentration or log concentration (if concentrations covers several decades). Residuals should be equally distributed between positive and negative values; it should not show any tendency.

(2) Visual observation of the trendline.

(3) Lack of fit test (F test)

In demonstrating linearity, standard solution replicates should be more than instrumental replicates. Calibration function can be plotted from minimum five concentrations in triplicate. F value is then calculated as follows (Araujo et al., 2009).

Sum of square due to residuals error (SSr2) = (back calculated response-individual response)$^2$. Back calculated response should take in to consideration calibration plot of average reading versus concentration.

Sum of square due to pure experimental errors (SSe2) = (Average response-individual response)$^2$.

Sum of squares due to lack of fit error (SSlof) = $SSr^2$ - $SSe^2$

Associated Variance due to residuals ($\sigma^2$r) = $SSr^2$ / dof = $SSr^2$ / Total readings – 2. In this equation value of 2 is derived from the equation used to demonstrate linearity. When equation y = mx + c is used, two parameters considered are m and c

Variance due to lack of fit ($\sigma^2$lof) = $SSlof^2$ / dof = $SSlof^2$ / Number of concentration levels-2

F ratio= $\sigma^2$lof / $\sigma^2$e at P of 0.050 with 95% confidence. F ratio should be small than F tabulated

(4) A test for significance of a quadratic coefficient b2 in a model, $y= b_o + b_1x + b_2 x^2$

(5) Divide signal data by their concentrations yielding the relative responses (*Figure 1*). These are plotted on y axis and corresponding log of concentration on x axis. Graph should be horizontal over the full linear range. A negative deviation is observed at higher concentration. Parallel horizontal lines drawn in the graphs corresponding to 95 and 105% of the horizontal line provides range.

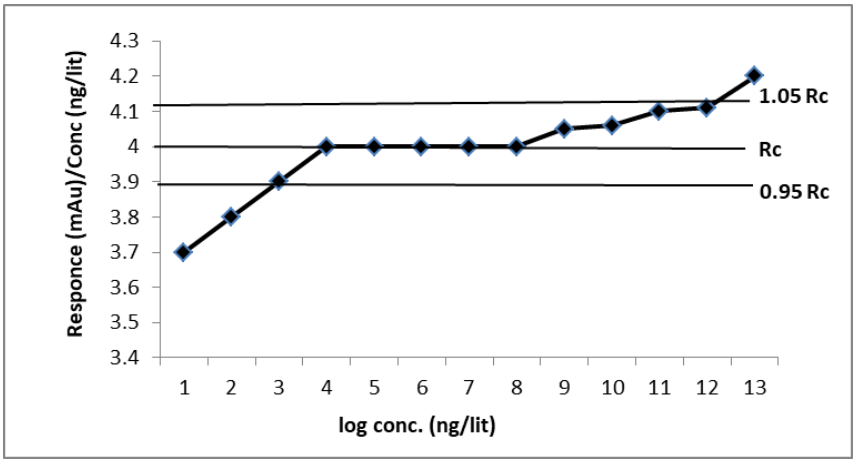


***Figure 1.*** *Linearity plot (Rc: Line Constant Response).*

It is not always necessary to get a linear relationship between analyte concentration and response. Other relationship may exist which may offer acceptable results. These should be considered before arriving to the final conclusion. The range of an analytical method is the interval between the upper and lower concentration of analyte in the sample for which it has been demonstrated that the analytical procedure has a suitable level of precision, accuracy and linearity.

## Materials and Methods

### *Limit of detection*

It is a point where a measured value is larger than the uncertainty associated with it. It is lowest concentration of analyte that can be detected but not necessarily quantified. Sensitivity is ability of method to consistently determine small amount of analyte (Taverniers et al., 2004; Vial and Jardy, 1999; Green, 1996).

### *Methods to determine LOD*

The Limit of detection is 3.3 X S. D. / S; where S.D.is standard deviation of y intercepts by multiple plotting of calibration curve or standard deviation of mobile phase response or standard deviation of blank or the residual standard deviation of the regression line.

(1) Based on S/N Ratio: It is the injected amount that gives response twice or thrice to that on noise.

(2) From blank response: LOD is calculated as either 2 or 3 times the variation in measured response.

(3) By Serial dilution/by visual detection: Standard solution is diluted serially upto the point where peak is lost.

(4) Based on standard deviation of y intercept: Value of the linear calibration curve's y-intercept.

### *Limit of quantitation*

It is lowest concentration which can be precisely and accurately quantified.

***Methods to determine LOQ***

(1) Based on S/N Ratio: It is the injected amount that gives response 10-20 times to that on noise.

(2) From blank response: LOD is calculated as either 10-20 times the variation in measured response.

(3) Based on standard deviation using following formula:

The Limit of Quantitation = 10 X S. D. / S

Where; S.D. is standard deviation of y intercepts by multiple plotting of calibration curve Or standard deviation of mobile phase response or standard deviation of blank or the residual standard deviation of the regression line

(4) Based on EURACHEM Method: Injection of each concentration with decreasing analyte concentration is done six times. A graph of % RSD against standard concentration can be plotted. Concentration interpolated from the previously defined precision is LOQ as shown in *Figure 2*.

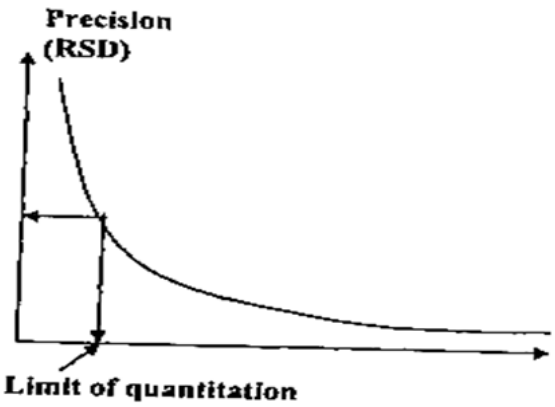


***Figure 2.*** *Limit of quantitation as per Eurachem method.*

***Accuracy***

It is degree of agreement in between the true value and value obtained by the method (González and Herrador, 2007). Accuracy of the method can be demonstrated by one of the following ways: (1) Methods results can be compared with the results obtained by established reference method; (2) Certified reference material can be analysed by the said method and a comparison with the test method is done; and (3) % Recovery-Sample or sample matrix can be spiked with standard analyte at 80, 100, 120% w/w of the test concentration. Recovery should be 98-102% w/w (individual) with 80, 100, 120% spiked sample. Blank sample matrix can be spiked with known concentrations of standard that cover range of concern. One should be close to the limit of quantitation and a substance should be added at early stage. Recovery may be affected by sample matrix, sample preparation procedure and analyte concentration. Accuracy should be assessed using a minimum of 9 determinations over a minimum of 3 concentration

levels covering the specified range (e.g., 3 concentrations/ 3 replicates each of the total analytical procedure).

## Results and Discussion

### *Robustness*

After performing intentional changes in the method parameters, the method results should remain unaffected (Papadoyannis and Samanidou, 2004). General Variables for HPLC method includes % organic content in mobile phase (+ 2%), pH of buffer in mobile phase (+ 0.5 pH units), column temperature (+ 1- 50 C), flow rate (+ 0.2 mL min-1). General parameters assessed are retention time, asymmetry factor, recovery and repeatability. One factor should be evaluated at a time, or they can be varied simultaneously as a part of factorial design. There should be no significant effect on assay. In the QbD approach, the robustness can be directly incorporated into the method qualities and evaluated during method development when selecting a design space and working points. Design space is basically a zone of theoretical robustness, because the modification or change of method conditions will not significantly affect the method quality.For the evaluation of robustness the DOE software can be utilized which through numerical optimization and graphical optimization of the experimental data gives information about Method Operable Design Region (MODR). For getting an experimental data for any analytical method, there is need to identify the purpose of the analytical method, Quality Target Method Profile (QTMP), define the CPP associated with the method. Risk assessment is performed to recognize CQA affecting robustness. Selection of design is dependent on number of dependant and independent variable associated with QTMP. The factors to be considered for QbD approach for robustness testing for various analytical methodsare given in *Table 2*.The variable factors include Number of theoretical plates, separation of all analytes, mobile phase (buffer an organic modifiers), elution method, sample concentration, sample diluent, sample solution stability, sample preparation process (dilution process, sonication time), filter, centrifuge, column type (stationary phase, dimension), detection, RRT, flow rate, injection volume, column oven temperature, runtime, system suitability parameters limits, LOD, LOQ, impurities calculation method, recovery establishment.

***Table 2.*** *QbD approach for method validation (Robustness testing).*

| Sr. No. | QTMP | Design to be applied (DOE) | Independent factors to be considered | Dependent factors to be considered |
|---|---|---|---|---|
| 1 | Column chromatography | Central Composite Design, Plackett-Burman Design, Full Factorial Design, Modified Factorial Design, Box Behnken Design | pH, Flow rate, Temperature of column, Injection volume, Composition of mobile phase, Percent of organic phase, Length of analytical column, Percentage of organic modifier, detection wavelength | Retention Time, Theoretical Plate Count, Tailing Factor, Retention Time |
| 2 | HPTLC | Central Composite Design, Optimal Design | Chamber saturation time, Percent of solvent, time between sample application to development, time between development to measurement, detection wavelength | Retention factor for drug , resolution, peak purity |

### *Publication trend in the chromatographic method development and validation using QbD approach*

The literature search was conducted in the month of August 2021 and literature from the period 2009–2021 was selected for this review. Literature pertinent to keywords such as HPLC, UPLC, HPTLC and QbD was retrieved from the Web of Science (WOS) core collection platform and SCOPUS database. Total 197 WOS and 199 SCOPUS literature was retrieved encompassing paid as well as non-paid articles of various categories such as research, review, short communications, and conference papers. The first paper using QbD in analytical method development appeared in 2009. Total 316 papers were found to be published in this area after duplication removal using conditional formatting of MS-Excel. The yearwise articles published are depicted in *Figure 3*. The papers published from 2020 are reviewed and summarized in *Table 3*.

***Table 1.*** *Summary of chromatographyic methods developed using QbD approach from 2020.*

| Sr. No. | Method | Critical quality attributes/independent variables | Response factors/dependent variables | Design of experiment | Reference |
|---|---|---|---|---|---|
| 1. | The Retention behaviour of structurally related β-blockers on RP-HPLC based on two complementary approach QbD and QSPR. | Temperatures of 26.00 and 27.50 C, pH 4.55, UV Detection at 220 nm | Retention time | Box-Behnken design. | Hakiem et al. (2021) |
| 2. | HPLC-QbD for simultaneons estimation of carisoprodol, paracetamol and caffeine. | Mobile phase composition, pH | Area, retention time, tailing factor, theoretical plates | 32 Full factorial design, Quadratic model was significant | Patel et al. (2021) |
| 3. | Systematic development and validation of a RP-HPLC method for estimation of abiraterone acetate and its degradation product. | Organic modifier (%), flow rate (mL.min−1) and autosampler temperature (◦C) | Area under peak, retention time, theoretical plate count and tailing factor | First screening carried out by Half-factorial design then optimized by Box-Behnken design. | Beg et al. (2021) |
| 4. | HPLC-DAD method for simultaneous determination of five Fluoroquinolone based antimicrobial drugs. | Mobile phase flow rate, column temperature and mobile phase. | Resolution, tailing factor, theoretical plates | Full factorial DOE using a minitab 17 statistical tool. | Asu et al. (2021) |
| 5 | Comprehensive stability-indicating method development of Avanafil using advanced QbD approach. | Mobile phase ratio, pH of the buffer, flow rate, and temperature of column | Resolution | Central composite design, From the Ishikawa diagram and risk assessment tool total, eleven primary parameters were selected and subjected to secondary parameter screening by Plackett–Burman design. | Patel and Kothari (2020a) |
| 6 | Multivariate analysis of Perampanel in Pharmaceutical formulations using RP-HPLC. | Concentration, pH of the phosphate buffer, temperature, flow rate and % of the aqueous part of mobile phase | Retention time, theoretical plates | Fractional factorial design | Elhawi et al. (2020) |
| 7 | Development of a green HPLC method for the | pH, temperature, and gradient slope | Resolution | Three level full factorial | Yabré et al. (2020) |

| | | | | | |
|---|---|---|---|---|---|
| | analysis of artesunate and amodiaquine impurities . | | | design | |
| 8 | RP-HPLC method for quantification of ferulic acid. | Mobile phase ratio and flow rate | Peak area, theoretical plate count, retention time and peak tailing | Taguchi design, Face-centred composite design | Saini et al. (2020) |
| 9 | UHPLC method for the Quantification of Perindopril, Amlodipine and their impurities in Pharmaceutical formulations | Flow rate, column temperature, perchloric acid concentration | Resolution | Response surface methodology. | Mohan et al. (2020) |
| 10 | Estimation of prucalopride succinate in the bulk and solid dosage form by RP-HPLC. | buffer pH, % Acetonitrile and flow rate | Retention time, number of theoretical plates, symmetry factor | Box-Behnken design. | Chawathe and Hamrapurkar (2020) |
| 11 | HPLC method for simultaneous quantification of Telmisartan and Hydrochlorothiazide impurities in tablets dosage. | Flow rate, Column temperature, Buffer pH | Resolution | Three level factorial design | Palakurthi et al. (2020) |
| 12 | Stability-indicating assay method for the estimation of Linezolid in Newly Developed Gelatin Nanoparticles for Anti-tubercular Therapy. | Organic solvent concentration in the mobile phase, pH ofmobile phase, solvent type, type of organic modifier, flow rate of mobile phase, injection volume and column type | Retention time, the number of theoretical plates, tailing factor | Risk assessment matrix and Taguchi orthogonal model<br>$3^3$ Box–Behnkendesign. | Patil et al. (2020) |
| 13 | Validated stability indicating and assay method development of linagliptin in formulation by RP-HPLC using quality by design. | Mobile phase aq, Mobile Phase org, Flow Rate, Wavelength and pH | Theoretical Plates, Tailing factor, Retention time | A three-level Box-Behnken design. | Gaonkar et al. (2020) |
| 14 | The application of quality by design in the development of the liquid chromatography method to determine empagliflozin in the presence of its organic impurities. | Flow rate, temperature, percent organic, pH | Number of plates, resolution, retention factor, retention time, and peak purity | Full factorial design | Manoel et al. (2020) |
| 15 | Strategies for stabilizing formulation and Qbd assisted development of robust stability indicating method of azilsartanmedoxomil/chlorthalidone. | pH, temperature, flow rate, and % of acetonitrile | Resolution, number of theoritical plates, run time | Central composite design | Gad et al. (2020) |
| 16 | Quality by design based development and validation of bioanalytical RP-HPLC method for dapagliflozin: Forced degradation and preclinical pharmacokinetic study. | Mobile phase composition, detection wavelength, flow rate | Area, retention time, tailing factor | Three levels and three-factor Box–Behnken statistical design | Ameeduzzafar et al. (2020) |
| 17 | Multivariate UV-chemometric and HPLC-QbD method for simultaneous estimation of vardenafil and dapoxetine in active pharmaceutical ingredients and its marketed formulation. | pH, temperature, mobile phase. | Retention time. | Box-Behnkendesign . | Patel and Kothari (2020b) |
| 18 | A QbD based study in development, optimization and forced degradation behaviour of epinastine hydrochloride in metered dose inhaler by RP-HPLC. | Mobile phase composition, and flow rate | Retention time. | $2^2$ central composite designs with response surface methodology. | Jena et al. (2021) |
| 19 | Quality assessment and RP- | pH of aqueous phase, | Tailing factor, peak | $2^2$ factorial | Parab Gaonkar |

| | | | | | |
|---|---|---|---|---|---|
| | HPLC method development for estimation of curcuminoids in Curcuma longa: A Quality by Design approach. | mobile phase ratio | width of all curcuminoids | design. | and Hullatti (2021) |
| 20 | Analytical Quality by Design Approach for a Stability-Indicating Method to Determine Apixaban and Its Related Impurities. | Column temperature, flow rate, mobile phase pH and organic percentage and chromatographic column as qualitative parameter | Resolution between each peak, analysis time, peak purity, retention factor and theoretical plate | Response surface methodology | Ellwanger et al. (2020) |

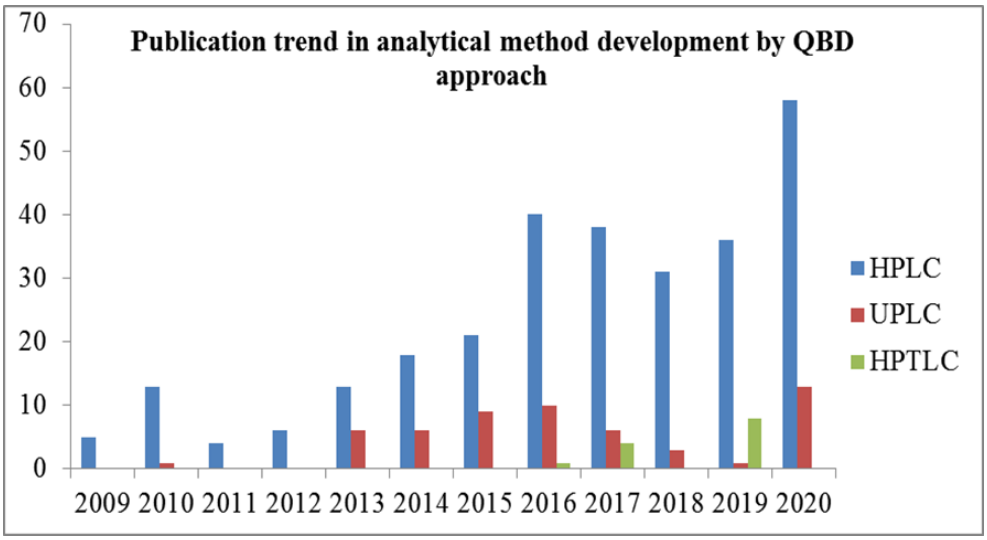


***Figure 3.*** *Publication trend in the chromatographic method development and validation using RbD approach.*

## Conclusion

There are various approaches used in validating various parameters of analytical method. The application of analytical Qbd helps in deep understanding and validation of analytical method which can provide assured separation of drugs, impurities, and other interfering matrix components more efficiently. It is a powerful decision-making tool for the robust analytical method development.

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## Conflict of interest

The authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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