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Analytical method validation: A brief review

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Abstract

Validation is an applied approach to verify that a method is suitable to function as a quality control tool. The objective of any analytical measurement is to obtain consistent, reliable and accurate data. Validated analytical methods play a major role in achieving this goal. An analytical method consists of the techniques, method, procedure and protocol. Analytical method validation includes the determination of accuracy, precision, LOD, LOQ, linearity and range. The results from method validation can be used to moderator the quality, reliability and consistency of analytical results, which is an integral part of any good analytical practice. Validation of analytical methods is also required by most regulations and quality standards that impact laboratories. The main objective of this review article is to guide the young researchers to improve the quality of analytical method development and validation process.

Keywords: Validation; Accuracy; Precision; Case study; Validation report

1. Introduction

The prime objective of any pharmaceutical plant is to manufacture products of requisite attribute and quality consistently, at the lowest possible cost [2]. Although validation studies have been conducted in the pharmaceutical industry for a long time, there is an ever increasing interest in validation owing to their industry's greater emphasis in recent years on quality assurance program and is fundamental to an efficient production operation. Validation is a concept that has evolved in United States in 1978. [8]

1.1. Definitions of Validation

According to FDA (FOOD AND DRUG ADMINISTRATION) VALIDATION is a procedure for production and process control designed to assure that the drug products have their identity, strength, quality and purity. According to FDA guidelines in May 1987, the validation package must provide the necessary information and test procedures required to prove that the system and the process meet the specified requirements. [14]

1.2. Importance of Validation

- Assurance of quality
- Time bound
- Process optimization
- Reduction of quality cost.
- Nominal mix-ups, and bottle necks
- Minimal batch failures, improved efficiently and productivity.

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- Reduction in rejections.
- Increased output.
- Avoidance of capital expenditures
- Fewer complaints about process related failures.
- Reduced testing in process and in finished goods.
- More rapid and reliable start-up of new equipment's
- Easier scale-up form development work.
- Easier maintenance of equipment.
- Improved employee awareness of processes.
- More rapid automation.

1.3. When does validation begin?

Ideally validation starts in the very beginning, in the laboratory. In the lab, scientists discover exactly how the product reacts, as well as the parameters that are required to produce such a product. They learn under what conditions the product fails or becomes unstable, unusable and when its quality begins to suffer. Once the laboratory has established the boundary processing criteria, this information can then be used for establishing requirements for validation.

1.4. When does validation ends?

Validation of a system never truly ends. Once a new system and process have been validated the system still requires maintenance, periodic calibrations and adjustment. Therefore, the process is always under scrutiny and constant evaluation.

1.5. Departments responsible

1.5.1. Site validation committee (SVC)

Develop Site Master Validation plan, Prepare/execute/approve validation Studies

1.5.2. Manufacturing department

Prepares the batches as a routine Production batch

1.5.3. Quality assurance

Ensure compliance, see that documentations/procedures are in place, approves protocols and reports

1.5.4. Quality control

Perform testing and reviews protocol and report as needed

Table 1 Responsible authorities for validation

Department /Designation	Responsibility
Manager Production	Responsible for manufacturing of batches and review of protocol and report.
Manager QC	Responsible for analysis of samples collected
Executive QC	Responsible for samples collection and submission to QC
Manager Maintenance	Providing utilities and engineering support
Executive Production	Responsible for preparation of protocol and manufacturing of validation batches
Manager QA	Responsible for protocol authorization and preparation of summary report.

1.6. Types of Validation

Validations are of different types which are given below:

- Process Validation
- Analytical Method Validation

- Cleaning Validation
- Computerized System Validation

1.7. Process Validation

The manufacturing process should be flexible with some restrictions during the process of manufacture of the product. The achievement of the alluring qualities should be ensured with the prevention of essential properties. For achieving these, process validation is performed. [9]

1.8. Goals of Process Validation

- It provides the guarantee for the assurance of the good quality which is required for the industry.
- For diminishing different batches variation.
- For saving time and money from retesting and reprocessing.
- For the process with the fulfilment of the criteria of robust.
- For consistent manufacture of the product and the process reproducibility.
- Declination of expenses due to product defect.
- For regulatory compliance.
- For the higher quality confirmation of the medicines

1.9. Analytical Method Validation

According to ICH Q2 (R1), method validation can be defined as, "Establishing a documented proof, which provides a high degree of assurance that a specific process will consistently produce a desired result at its prearranged specifications and quality characteristics."

Simply, it is the process of indicating that analytical procedures are suitable for their planned use and that they support the identity, quality, purity, and potency of the drug substances and drug products. Method Validation is requiring when a new method has been developed and when established methods are used in different laboratories and different analysts.

The performance characteristics required to validate various methods by using various guidelines such as USP, ICH, FDA, European guidelines etc. [10, 11]

1.9.1. According to USP

The analytical parameters can be validated are accuracy, precision, specificity, detection of limit, quantitation limit, linearity, range, ruggedness and robustness.

1.9.2. According to ICH

The analytical parameters can be validated are accuracy, precision, specificity, detection of limit, quantitation limit, linearity, range, system suitability and robustness.

1.9.3. According to FDA

The analytical parameters can be validated are accuracy, precision, specificity/selectivity, detection of limit, quantitation limit, linearity, range, system suitability, reproducibility, sample solution stability and robustness.

1.9.4. According to European guidelines

The analytical parameters can be validated are accuracy, precision, specificity, detection of limit, quantitation limit, linearity and range.

Analytical methods need to be validated, verified, or revalidated in the following instances:

- Before initial use in routine testing
- When transferred to another laboratory
- Whenever the conditions or method parameters for which the method has been validated change (for example, an instrument with different characteristics or samples with different matrix).

1.10. Types of analytical procedures to be validated

The following types analytical procedures to be validated. [3]

- Identification tests
- Quantitative tests for impurities content
- Limit tests for the control of impurities
- Quantitative tests of the active moiety in samples of drug substance or drug product.

1.10.1. Identification tests

Identification tests are used to ensure the identity of an analyte in a sample. This is normally achieved by comparison of a property of the sample (e.g., spectrum, chromatographic behavior, chemical reactivity, etc.) to that of a reference standard.

1.10.2. Quantitative tests and Limit tests for impurity control

Testing of impurities can be performed by using a quantitative test or a limit test for the impurity in a sample. Different validation parameters are required for a quantitative test than for a limit test;

1.10.3. Quantitative tests of the active moiety in samples of drug substance or drug product

In this type, assay procedures are used to measure the analyte present in a given sample. The assay represents a quantitative measurement of the major component(s) in the drug substance.

2. Objectives and advantages of method validation [4]

Objectives

- To obtain consistent, reliable and true data.
- To demonstrate that it is suitable for its intended purpose.
- To form a base for written procedure for production and process control which are designed to assure that the drug products have the identity, strength, quality and purity.
- To hold the quality, safety and efficacy in final product.
- To control each step of manufacturing process.
- To produce the best analytical results possible.

Advantages

- It builds a degree of confidence, not only for the developer but also to the user.
- Produces quality products.
- Reduce the product cost by increasing efficacy, few reject and longer equipment life.
- Helps in optimization of process or method.
- Helps in process improvement, technology transfer related products validation and increased employee awareness.
- It eliminates testing repetitions and leads to better time management in the end.

3. Steps involved in method validation. [4]

The preparation and implementation should follow a validation protocol, preferably written in a step by step instruction format

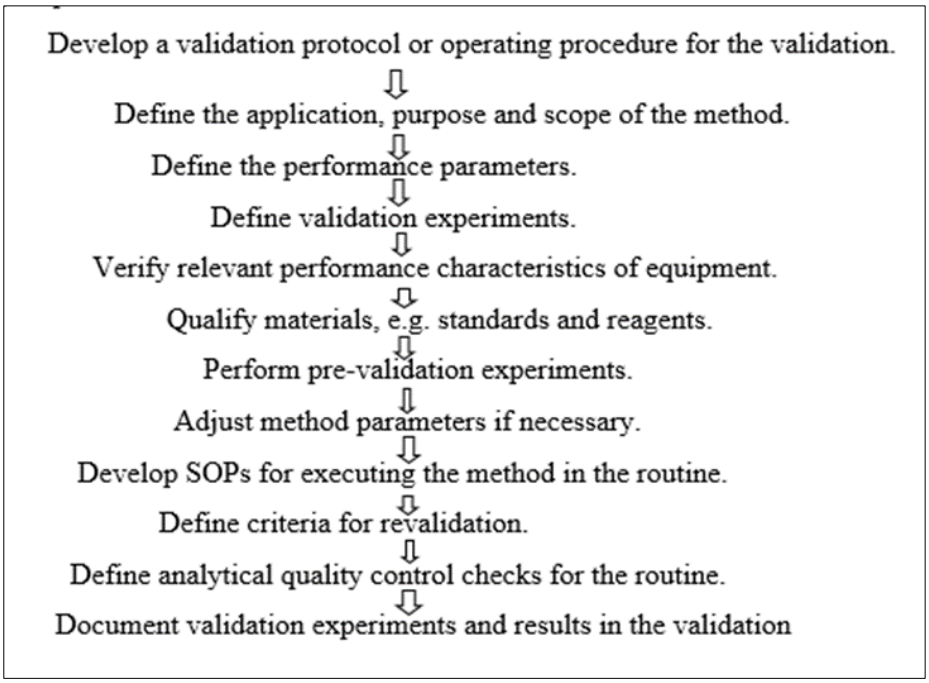

Figure 1 Steps involved in method validation. [4]

4. Key parameters of the analytical method validation. [1,4]

It is important for to understand the parameters or characteristics involved in the validation process. The various performance parameters, which are grouped as follows,

- Accuracy
- Precision
  - Repeatability
  - Intermediate precision
  - Reproducibility
- Specificity/Selectivity
- Limit of Detection (LOD)
- Limit of Quantitation (LOQ)
- Linearity
- Range
- Robustness
- Ruggedness
- System suitability testing.

4.1. Accuracy

Accuracy of an analytical method may be defined as, “Closeness of test results obtained by the method to true value”. i.e. measure the exactness of analytical method. It is expressed as percent recovery by the assay of known amount of analyte in the linearity range.

4.1.1. Determination methods

Application of analytical method to an analyte of known concentration

The accuracy may be determined by application of the analytical method to an analyte of known purity (example: reference standard) and also by comparing the results of the method with those obtained using an alternate procedure that has been already validated

Spiked – placebo recovery method

In this method, a known amount of pure active constituents is added to formulation blank (sample that contains all other ingredients except the active) and then perform the assay of resulting mixture and compare the obtained results with predictable results.

Standard addition method

In this method, perform the assay of given sample, then add a known amount of active constituent to that assayed sample. After that this sample is again assayed. The difference between the results of the two assays is compared with the expected results.

Recommended Data
ICH document recommend that accuracy should be measured using a minimum of nine determinations per 3 concentration level.

Acceptance criteria
The mean value should be within 15% of the supposed value except at LLOQ, where it should not deviate by more than 20%. The deviation of the mean from the nominal value serves as the measure of accuracy.

4.2. Precision

The precision of an analytical method may be defined as, "Closeness of agreement between a series of measurements obtained from multiple sampling of the same standardized sample under the prescribed conditions."

- Should be investigated using homogeneous, authentic samples.
- Expressed as SD/ RSD

$$\% \text{ RSD } = \frac{\text{Standard Deviation}}{\text{Mean}} \text{x } 100$$

Precision…….. considered at 3 levels,

4.2.1. Repeatability

It expresses the precision under the same operating conditions over a short interval of time. i. e analysis of replicates by the analyst using the same equipment and method.

4.2.2. Intermediate precision

It expresses the precision within laboratories variations. i. e different days, different analyst, and different equipment's etc. It is not necessary to study effects individually.

4.2.3. Reproducibility precision

It expresses the precision between laboratories (two-way studies, usually applied to standardization of method) for addition of procedures in pharmacopoeias. i.e Validation of tests for assay and for quantitative determination of impurities includes an investigation of precision.

4.2.4. Recommended Data

The standard deviation, relative standard deviation and confidence interval should be reported for each type of precision investigates.

4.2.5. Acceptance criteria

The precision determined at each concentration level should not exceed 15% of the coefficient of variation (CV) except for the LLOQ, where it should not exceed 20% of the CV.

4.3. Specificity

ICH defines specificity of an assay is the ability to measure accurately and specifically the analyte in the presence of other components that may be expected to present in the sample medium. The term specific generally refers to a method that produces a response for a single analyte only.

ICH document divides specifically in to three categories.

4.3.1. Identification tests

To ensure the identity of an analyte.

4.3.2. Purity tests

To ensure that all analytical procedures performed allow an accurate statement of the content of impurities of an analyte, i.e. related substances test, heavy metals etc.

4.3.3. Assay

To provide an exact result which allows an accurate statement on the content or potency of an analyte in a sample?

4.4. Selectivity

Selectivity of method to detect the analyte in the presence of components that may be expected to be present in the sample matrix. Simply it is the ability of a separative method to resolve different compounds. It is the measure of the relative method location of two peaks. It is the method that provides responses for a number of chemical entities that may or may not be separated from each other. It is determined by comparing the test results obtained on the analyte with and without addition of potentially interfering material.

4.5. Limit of detection

The limit of detection of an analytical procedure is the lowest amount of an analyte in a sample that can be detected, but not necessarily quantify under stated experimental conditions. Simply it indicates that the sample is below or above certain level. The LOD will not only depend on the procedure of analysis but also on type of instrument.

4.5.1. Measurement is based on

- Visual evaluation.
- Signal to noise ratio.
- The standard deviation of the response and the slope.

Visual evaluation

LOD is determined by the analysis of samples with known concentration of analyte and by establish the minimum level at which the analyte can be detected. It can be used for instrumental and non-instrumental procedure.

Signal to noise ratio

This approach can only be applied to analytical procedure which shows baseline noise. It is performed by comparing measured signals from samples with known low concentration of analyte with those of blank samples and establishes the minimum concentration at which the analyte can be detected.

Signal to noise ratio 2:1 or 3:1 is generally accepted.

The standard deviation of the response and the slope

$$\text{LOD} = \frac{3.3\sigma}{\mathbf{S}}$$

σ = Standard deviation of the response.

S = Slope of the calibration curve of the analyte from regression line.

4.6. Limit of quantitation

The LOQ is the lowest amount of analyte in a sample which can quantitatively determine that may be measured with an acceptable level of accuracy and precision under the stated operational conditions of the method. LOQ can vary with the type of method employed and the nature of the sample. It is generally used for the determination of impurities or degradation products.

4.6.1. Measurement is based on

- Visual evaluation.
- Signal to noise ratio.
- The standard deviation of the response and the slope.

Visual evaluation

LOQ is determined by the analysis of samples with known concentration of analyte and by establish the minimum level at which the analyte can be detected. It can be used for instrumental and non-instrumental procedure.

Signal to noise ratio

This approach can only be applied to analytical procedure which shows baseline noise. It is performed by comparing measured signals from samples with known low concentration of analyte with those of blank samples and establishes the minimum concentration at which the analyte can be detected. Signal to noise ratio 10:1 is generally accepted.

The standard deviation of the response and the slope

$$\text{LOD} = \frac{10\,\sigma}{\mathbf{S}}$$

σ = Standard deviation of the response.

S = Slope of the calibration curve of the analyte from regression line.

4.7. Linearity

Linearity is the ability of the method to obtained test results that are directly proportional to the analyte concentration within a given range. A linear relationship should be evaluated across the range of the analytical procedure. It may be established directly on the drug substance by dilution of a standard stock solution. Linearity should be evaluated by visual inspection of a plot a graph of concentration (on x - axis) Vs mean response (on Y - axis). Calculate the regression equation, Y- intercept and correlation coefficient. Data from the regression line itself may be helpful to provide mathematical estimates of the degree of linearity. For the determination of linearity, a minimum of 5 concentrations is recommended.

4.8. Range

Range of analytical procedure 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. Normally derived from linearity studies and specific range is dependent upon proposed application of the procedure.

The following minimum specified ranges should be considered:

- Assay of a drug substance or a finished (drug) product: 80 to 120 % of the test concentration.
- Content uniformity: 70 to 130 % of the test concentration.
- Dissolution testing: +/-20 % over the specified range;

4.9. Robustness

It is the measure of the capacity of the analytical method to remain unaffected by small but deliberate changes in procedure to provide an indication about variability of the method during normal laboratory conditions.

4.9.1. Examples of typical variations are

- Stability of analytical solutions;
- Extraction time.

4.9.2. In the case of liquid chromatography, examples of typical variations are:

- Influence of variations of pH in a mobile phase;
- Influence of variations in mobile phase composition;
- Different columns;

- Temperature;
- Flow rate.

4.9.3. In the case of gas-chromatography, examples of typical variations are:

- Different columns;
- Temperature;
- Flow rate.

4.10. Ruggedness

Degree of reproducibility of test results obtained by analyzing the same sample under variety of normal test conditions such as different.

- Analysts
- Instruments
- Days
- Reagents
- Columns and TLC plates.

i.e. lack of influence of environmental variables on the method. Comparison of reproducibility of test results to the precision of assay is the direct measure of ruggedness of the method.

4.11. System suitability testing

System suitability testing is an integral part of many analytical procedures. Once the method or system has been validated the task becomes one of checking the suitability of the system to perform within the validated limits. The tests are based on the concept that the equipment, electronics, analytical operations and samples to be analyzed constitute an integral system that can be evaluated as such. System suitability test parameters to be established for a particular procedure depend on the type of procedure being validated. The simplest form of an HPLC system suitability test involves a comparison of the chromatogram trace with standard.

5. Statistics in Analytical Method Validation [7]

Statistical investigation of data obtained during a method validation should be performed to reveal validity of the analytical method. The statistics required for the interpretation of analytical method validation results are the computation of the following-

- Mean
- Standard deviation
- Relative standard deviation
- confidence intervals
- Regression analysis.

These calculations are classically performed using statistical software packages such as Excel, Minitab, etc. The purpose of statistical analysis is to review a collection of data that provides an understanding of the examined method characteristic. The approval criterion for each validation characteristic is typically around the individual values as well as the mean and relative standard deviation.

5.1. Mean

Mean or average of a numbers set is the essential and the most frequent statistics used. The mean is calculated by adding all data points and dividing the sum by the number of samples. It is typically denoted by $\bar{x}$ (x bar) and is computed using the following formula:

$$\overline{x} = \frac{\sum X_i}{n} = \frac{X_1 + X_2 + X_3 + \cdots}{n}$$

Where X_i are individual values and n is the number of individual data points.

5.2. Standard Deviation

The standard deviation of a data set is the evaluation of the spread of the values in the sample set and is computed by measuring the variation or difference between the mean and the individual values in a set. It is expressed using the following formula:

$$s = \sqrt{\frac{\sum_i (X_i - \bar{X})^2}{n-1}} = \sqrt{\frac{(X_1-\overline{X})^2+(X_2-\overline{X})^2+(X_3-\overline{X})^2+\cdots}{n-1}}$$

Where X_i is individual value, $\bar{X}$ is the sample mean and n is the number of individual data points.

5.3. Relative Standard Deviation

The relative standard deviation is computed by taking the standard deviation of the sample set multiplied by 100% and dividing it by the sample set average. The relative standard deviation is expressed as percent. Typically, the acceptance criterion for accuracy, precision, and repeatability of data is expressed in % RSD:

$$\%\ \text{RSD} = \frac{s}{\bar{X}} * 100\%$$

5.4. Confidence Interval

Confidence intervals are used to indicate the reliability of an estimation. Confidence intervals gives us limits around the sample mean to predict the range of the true population of the mean. The prediction is usually based on possibility or probability of 95%. The confidence interval depends on the sample standard deviation and the sample mean.

$$\mu = \bar{X} \pm \frac{zs}{\sqrt{n}}$$

Where s is the sample deviation, $\bar{X}$ is the sample mean, n is the number of individual data points, and z is constant obtained from statistical tables for z. The value of z depends on the confidence level listed in statistical tables for z. For 95%, z is 1.96. For small samples, z can be replaced by t-value obtained from the Student's t-distribution tables. The value of t corresponds to n-1.

5.5. Regression Analysis

Regression analysis is used to evaluate a linear relationship between test results. A linear relationship is usually evaluated across the range of the analytical practice. The data obtained from analysis of the solutions prepared at a range of different concentration levels is usually investigated by plotting on a graph. Linear regression evaluates the relationship between two variables by fitting a linear equation to experimental data. A linear regression line has an equation of the form-

$$\mathbf{Y = b_o + b_1X},$$

Where,

X- Independent or self-determining variable and

Y - Dependent variable.

The slope of the line is $\mathbf{b_1}$, and $\mathbf{b_o}$ is the intercept (the value of **y** when **x** = 0). The statistical procedure of ruling the "best-fitting" straight line is to obtain a line through the points to reduce the deviations of the points from the approaching line. The best-fit criterion of integrity of the robustness or fitness is known as the principle of least squares.

6. A Case study

Method development and validation of Paracetamol drug by RP – HPLC. [5]

6.1. Abstract

A simple and reproducible method was developed for paracetamol by Reverse Phase High Performance Liquid Chromatography (RP-HPLC). Paracetamol was separated on C18 column [4.6x250mm, particle size 5µm], using ortho phosphoric acid buffer with pH of 3.5 at the UV detection of 207nm. Isocratic elution of acetonitrile (ACN) and water was used as a mobile phase with various ratios and flow rates, eventually 25:75 v/v ACN and water was being set with the flow rate of 1mL/min. The statistical validation parameters such as linearity, accuracy, precision, inter-day and intra-day variation were checked, further the limit of detection and limit of quantification of paracetamol concentrations were found to be 120ng/mL and 360ng/ml. Recovery and assay studies of paracetamol were within 99 to 102% indicating that the pro-posed method can be adoptable for quality control analysis of paracetamol.

6.2. Validation of the method

Validation of the optimized HPLC method carried out with the following parameters,

6.2.1. Linearity

Paracetamol standard stock solution of 10mg/mL was used for preparation of subsequent aliquots; aliquots of 100, 50, 25, 12.5 and 6.25 µg/mL concentrations were prepared by serial dilution. The solution of 200 µL was loaded in autosamplar tray and 20 µL was being injected into column. All measurements were repeated three times for each concentration. The calibration curves of the area under curve versus concentration were recorded.

6.2.2. Accuracy

Paracetamol standard stock solution of 10mg/mL was used to prepare 10, 35, 55 µg/mL concentrations and injected for the accuracy studies. The area under curve obtained was checked and analyzed for the recovery percentage.

6.2.3. Precision

The precision of method was checked and verified by repeatability, inter-day and intra-day precision. Repeatability was checked by injecting 80 g/mL concentration of paracetamol for 6 times on the same day and for intraday precision one concentration was injected and analyzed at different time intervals on the same day. Similarly, for the inter-day precision another concentration was analyzed on different days.

6.2.4. LOD and LOQ

The LOD and LOQ of paracetamol were separately determined on the basis of signal (S) and noise (N) ratio, LOD and LOQ concentrations of paracetamol were confirmed and recorded by the S/N ratio where 3 and 9 were shown.

6.2.5. Robustness of the method

To determine the robustness of the developed method, minute changes were made in the flow rate, percentage of ACN and the pH of the mobile phase and is studied for the deviations from optimized method.

6.3. Result and Discussion

The developed and validated method of paracetamol was aimed to establish chromatographic conditions, capable of qualitative and quantitative determination of paracetamol in pharmaceutical preparations. Paracetamol was completely separated on C18 column by RP-HPLC using the isocratic elution of ACN and water as mobile phase. It is evident that the flow rate of mobile phase in chromatography plays an important role in resolving the paracetamol, as the flow rate in-creases from 0.75 mL/min to 1.50 mL/min the retention time also decreased with fluctuation in paracetamol recovery, eventually proper resolution was achieved at flow rate.

6.3.1. Linearity

The method gave a linear response to paracetamol drug within the concentration range of 6.25 - 100 µg/mL with r2= 0.999 as shown in figure 2

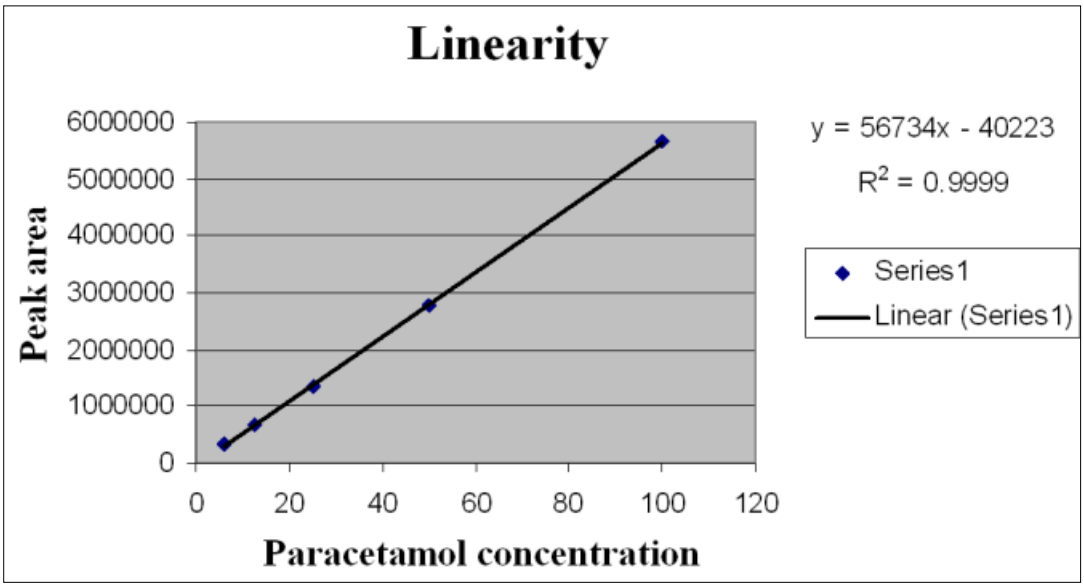

Figure 2 Linear response of peak area against paracetamol concentration. [5]

6.3.2. Accuracy

The paracetamol was recovered in the range of 98.8 to 102.0 % for various concentrations as shown in the table 2,

Table 2 Recovery percentage of Paracetamol

Concentration. (ug/ml)	Area	Amount recovered	Recovery (%)
10	520308	09.88	98.8
35	1963621	35.32	100.9
55	3143689	56.12	102.0

6.3.3. Precision

The repeatability, intra-day and precision results are shown in the table 3. The RSD values were below 3%, indicating a good precision. The t-test value for inter-day precision was less than 0.1%, indicating the significant precision.

Table 3 Developed method was checked for precision with different intervals Repeatability

Injection No.	Area	Amount Recovered	Recovery %
1	4498501	80.00	100.00
2	4517340	80.33	100.40
3	4527683	80.69	100.86
4	4575290	81.35	101.68
5	4602753	81.83	102.28
6	4624520	82.22	102.77

Table 4 Intra-day precision

Time (hrs)	Concentration (µg/mL)	Mean of area	SD	RSD
0	25	1352231	15349	1.13
3	25	1357626	7423.9	0.54
0	50	27796225	44542	1.60
3	50	2767559	27159.2	0.98

6.3.4. LOD and LOQ

The LOD and LOQ concentrations of paracetamol were found to be 120 ng/mL and 360 ng/mL.

6.3.5. Robustness of the method

The robustness of the method gave the mean, standard deviation (SD) and RSD within the limits.

7. Validation Report

Once the method has been developed and validated, a validation report should be prepared. The report should include sufficient information so that an experienced analyst can repeat the validation study. Typically, it should include the following:

- Purpose and scope of the method (applicability, type)
- Summary of methodology
- Responsibilities
- Type of compounds and matrix
- All chemicals, reagents, reference standards, QC samples with purity, grade, their source, or detailed instructions on their preparation
- Procedures for quality checks of standards and chemicals used
- Safety precautions
- A plan and procedure for method implementation from the method development lab to routine analysis
- Critical parameters taken from robustness testing
- Detailed parameters and conditions on how the experiments were conducted, including sample preparation and method parameters
- Statistical procedures and representative calculations
- Procedures for QC in routine analyses, such as system suitability tests
- Representative plots, such as chromatograms, spectra and calibration curves including raw data
- Method acceptance limit performance data
- Criteria for revalidation
- Qualification records of the individuals who developed and validated the method.
- References, if necessary
- Deviations from the validation plan and protocol
- Summary and conclusions
- Approval with names, titles, date and signatures of those responsible for the review and approval of the analytical test procedure

8. Conclusion

Analytical method validation playing a main role in pharmaceutical industry. The main objective of this review article is to guide the young researchers to improve the quality of analytical method development and validation process. This article gives whole idea about the analytical method validation. The results from method validation can be used to moderator the quality, reliability and consistency of analytical results, which is an integral part of any good analytical practice. The optimized reverse phase HPLC method for paracetamol is linear, accurate, precise, robust, simple, rapid and selective. It can be adopted apparently for routine quality control analysis of raw materials, formulations and testing.

Compliance with ethical standards

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Disclosure of conflict of interest

There are no conflicts of interest.

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