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A Review on: Analytical Method Development and Validation and It's QbD Approach

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Abstract

The top objective of any pharmaceutical industry is to produce products of necessary characteristic and quality reliably, in a cost-effective manner. The main aim of this review article was to check the development and validation of the procedure employed for the medication from the starting of the formulation to the complete commercial batch of product and different steps involved in method development by the QbD approach for analytical method development and describes the implementation of QbD in analytical procedure validation. High performance liquid chromatography is most accurate methods widely used for the qualitative and quantitative analysis of drug product. HPLC is an analytical tool which is able to detect, separate and quantify the drug, its various impurities and drug related degradants that can be generate on synthesis or storage. Method development is essential for discovery and evaluation of drugs in the pharmaceutical formulation. HPLC method development depends on chemical structure of the molecules, synthetic route, solubility, polarity, pH and pKa values, and functional groups activity etc. functional groups activity etc. Validation of HPLC method as per ICH Guidelines gives information regarding various stages and knowing characteristics like Accuracy, specificity, linearity, limit of detection, ruggedness, robustness limit of quantification. Quality by Design (QbD) is a methodology of pharmaceutical development, recommended by regulatory agencies like USFDA. QbD helps in building the quality of products by design through risk assessment at the early stage and defining the design space at the later stage QbD based product development enables the understanding of additional formulation aspects by using a scientific approach and quality risk management.

Keywords: - Method development, Validation, HPLC, QbD, Analytical QbD

Introduction

The High Performance Liquid Chromatography (HPLC) is one of the most powerful tool in analytical chemistry. It has ability to identify, separate and quantify the compounds that are present in any sample that can dissolved in a liquid. The HPLC is most accurate method which is widely used for quantitative and qualitative analysis of drug product and used for analyze and determine the stability of drug product.(1)

High Performance Liquid Chromatography (HPLC) was derived from the classical column chromatography and, is one of the most important tools of analytical chemistry today. Analytical chemistry deals with methods for identification, separation, and quantification of the chemical components of natural and artificial materials.(2) The analytical chemistry is used for the study qualitative and quantitative composition of material. These both aspects are necessary to understand the sample material. Analytical chemistry has been divided into two branches quantitative and qualitative. A qualitative analysis gives us the information about the nature of sample by knowing about the presence or absence of certain components. A quantitative analysis provides numerical information as to the relative amount of one or more of these components. For the analyzing drug sample in bulk, Pharmaceutical formulation the different analytical methods are routinely being used. (3)

In the modern pharmaceutical industry, high performance liquid chromatography (HPLC) is the major and integral analytical tool which is applied in all stages of drug discovery, development, and production. The HPLC one of the best methods used for checking peak purity of new chemical entities, monitoring reaction changes in synthetic procedures or scale-up, evaluating new formulations and carrying out quality control as well as assurance of the final drug product. The goal of the HPLC method is to separate and quantify the main drug, any reaction impurities, all available synthetic intermediates and any degradants.(4)

Classification of analysis(5)

The analysis for method development and validation can be classified in two types Quantitative analysis and Qualitative analysis

Qualitative analysis

The qualitative analysis in which substances are identified or classified on the basis of their chemical or physical properties, such as chemical reactivity, solubility, melting point, molecular weight, radiative properties, mass spectra, etc. The Qualitative Analysis can take place without Quantitative Analysis, but Quantitative Analysis requires the identification (qualification) of the analyze for which numerical estimates are given.(6)

Quantitative analysis

The quantitative analysis in which the amount or concentration of an analyte may be determined (estimated) and expressed as a numerical value in appropriate units. Qualitative Analysis may take place without Quantitative Analysis, but Quantitative Analysis requires the identification (qualification) of the analytes for which numerical estimates are given.(7)

Introduction to chromatography

A method of separating and identifying the components of a complex mixture by differential movement through a two-phase system, in which the movement is affected by a flow of a liquid or a gas (mobile phase) which percolates through an adsorbent (stationary phase) or a second liquid phase. "Chromato" "graphy" derives its name from two words as chromo means colour and graphy means to write i.e., colour bands are formed in the procedure which are measured or analyzed. These colour bands are formed due to the separation of individual compounds. Chromatography is a widely used method for the separation , identification and determination of the chemical components in complex mixtures.(8,9)

Types of chromatography

- Paper chromatography
- Column chromatography
- Thin layer chromatography
- Gas chromatography
- Ion exchange chromatography
- Two-dimensional chromatography
- High performance (pressure) liquid chromatography
- High pressure thin layer chromatography

HPLC Principle

The main principle involved in HPLC is adsorption. The solution of the sample is injected into a column of a porous material (stationary phase) and a liquid (mobile phase) is pumped at high pressure through the column. The separation of sample is based on the differences in the rates of migration through the column arising from different partition of the sample between the stationary and mobile phase.(10,11)

When a mixture of components is introduced into a HPLC column, they travel according to their relative affinities towards the stationary phase. Depending upon the partition behavior of different components, elution takes place at different times. The component which has more affinity towards the adsorbent travels slower. The component which has less affinity towards the stationary phase travels faster.(12)

The technique of HPLC has following features.(13)

- High resolution
- Rapid analysis
- Controlled flow rate of mobile phase
- Small diameter, Stainless steel, Glass column
- High sensitivity
- High accuracy
- Easy to purify the sample
- Relatively high inlet pressure and controlled flow of mobile phase
- Ease of automation
- Good repeatability
- Simultaneous Analysis

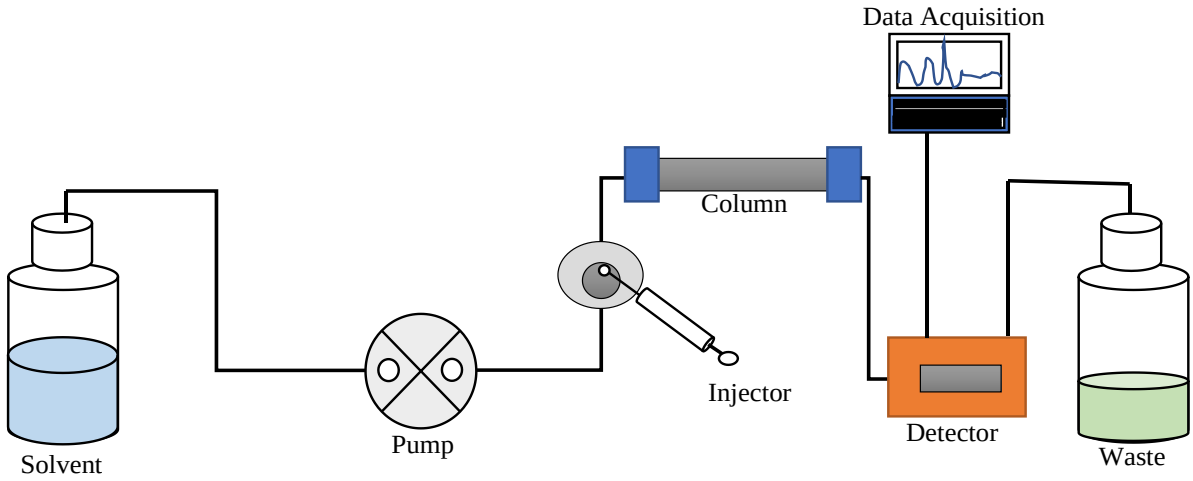

Fig 1: - Flow diagram of HPLC

Analytical method development

Analytical method development is the process of developing a specific analytical method for drug products from the in-process to finished product stage, as well as validation to be done prior to beginning analyses of routine samples, investigation samples, and stability samples. Analytical method development and validation are critical steps which plays important roles in the discovery, development and manufacture of pharmaceuticals. These techniques are used to ensure the identity, purity, potency, and performance of pharmaceutical products. Development and validation of analytical methods can provide accurate, reliable, and coherent data. Procedures for developing methods are expensive, complex, and time-consuming. A method of analysis specifies the steps and techniques required for carrying out an analysis. This may include preparing samples, standards, and reagents, using equipment, etc. (14,15)

Development and Validation of an analytical method provides accurate, reliable and coherent data. Method development procedures are costly, complex, and time-consuming. A method of analysis outlines the steps and techniques needed to conduct an analysis. This may include preparing samples, standards, and reagents, as well as operating equipment.(16,17)

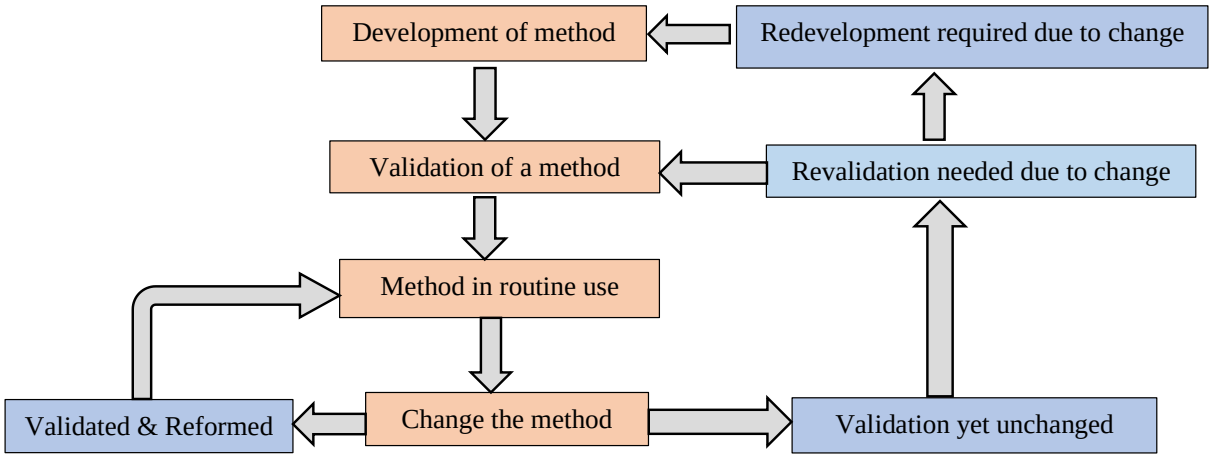

Fig 2:- The lifecycle of an analytical method

Need of method development

When there are no definitive techniques are present then the new methods are developed to evaluate new products. To investigate the existence of pharmacopoeial or non-pharmacopoeial products, new techniques are being developed that reduce the value besides time for higher precision and strength.(18) These methods are optimized and valid through preliminary runs. Alternative ways are planned and place into practice to exchange the present procedure within the comparative laboratory information with all available merits and demerits. The principle purpose of analytical method development is to generate data regarding efficiency, impurity, bioavailability, stability and effect of manufacturing parameters to verify that the production of drug is steady.(19,20)

The new method should be developed when:(21)

- Available method is be too expensive, time consuming, or that may not be easily automated
- Existing method has been too much error, contamination prone or they may be unreliable.
- There may not be a suitable method for a particular analyte in the specific sample matrix.
- There may be need for an alternative method to confirm, for legal or scientific reasons, analytical data originally obtained by existing methods.
- For regulatory requirements it is required.
- Existing method may not provide adequate sensitivity
- Newer instrumentation and techniques may have evolved that provide opportunities for improved methods, including improved analyte identification or limit of detection, greater accuracy or better return on investment

HPLC method development

When there are no approved methods for a new product, methods are developed. Alternative methods for existing products include reducing cost manufacturing time in exchange for greater precision and robustness. When an alternate approach is recommended to replace an existing procedure, comparative laboratory data, including benefits and demerits, is made accessible. The HPLC-method attempts to extract and quantify the main active drug, any reaction contaminants, any available synthetic intermediates, and any degradants.(22)

The following steps are involved in HPLC method development

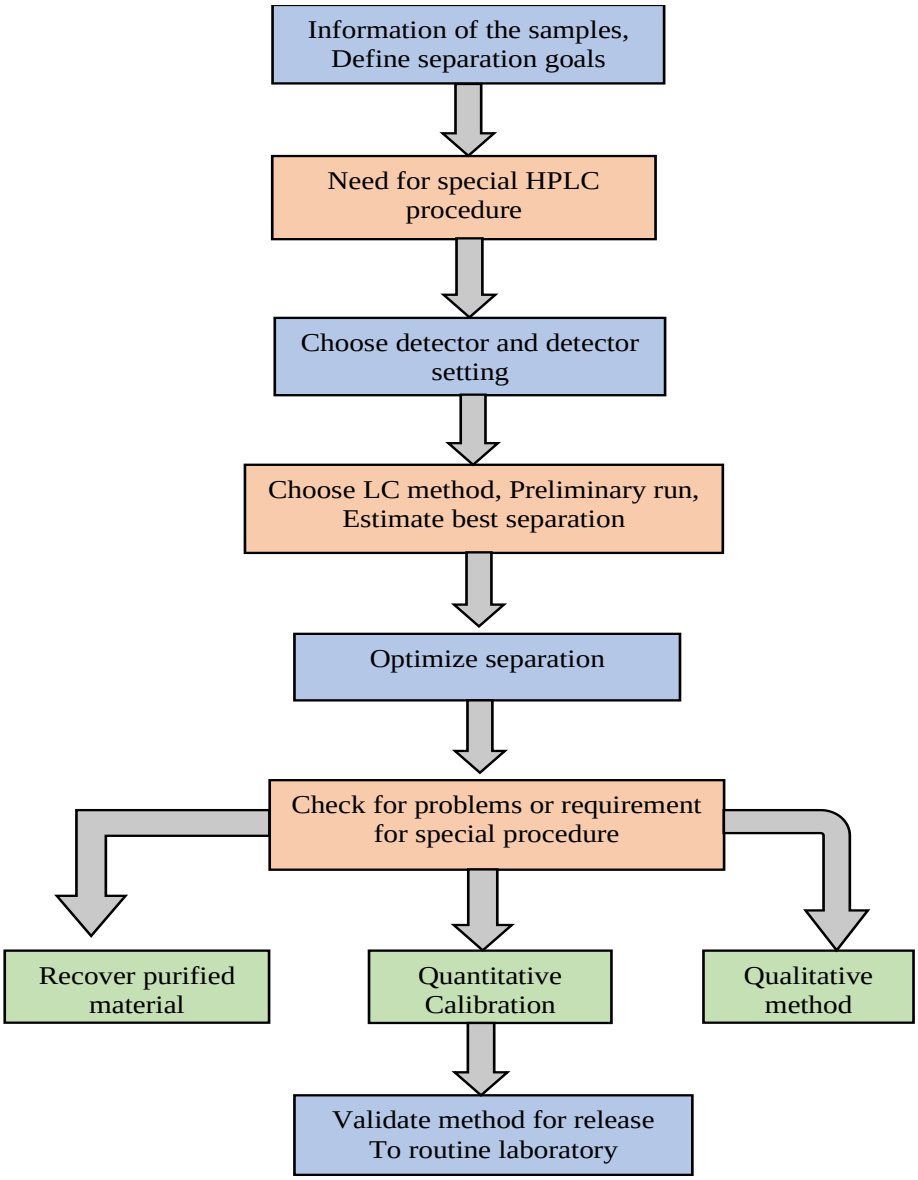

Fig 3:- Steps involved in HPLC method development

Physicochemical properties of drug:

The physicochemical properties of a drug molecule are plays critical role in method development. To create a method, one must first investigate the physical properties of the drug molecule, such as solubility, polarity, pKa, and pH. Polarity is a physical property of a compound. It assists an analyst in determining the solvent and mobile phase composition. The electrons in a non-polar covalent bond are shared equally between two atoms. A polar covalent bond is one in which one atom is more attracted to electrons than the other. The polarity of molecules can be used to explain molecular solubility. Polar solvents, such as water, and non-polar solvents, such as benzene, do not combine. In general, like dissolves like, which means that elements with similar polarities are soluble in each other. The solubility of the analyte is used to select diluents. The analyte must be soluble in the diluents and must not react with any of them. The diluent should match to the starting eluent composition of the assay to ensure that no peak distortion will occur, especially for early eluting components. pH and pKa plays an important role in HPLC method development.(23,24)

Selection of chromatographic conditions:

During initial method development, a set of initial conditions (column, mobile phase and detector) is selected. In most cases, these are based on re- versed-phase separations on a C18 column with UV detection. A decision on developing either an isocratic or a gradient method should be made at this point.(25)

It includes:

- **Selection of column**

The column is the heart of an HPLC system. During method development, changing a column will have the largest impact on analyte resolution. A properly chosen column can give accurate and reliable analysis as well as good chromatographic separation. An incorrectly used column can frequently cause confusion, difficulties, and poor separations, which can lead to results that are invalid or complex to interpret. The stationary phase can be supported by a variety of matrices, including silica, polymers, alumina, and zirconium. The most commonly used matrix for HPLC columns is silica. Silica matrices are strong, easily derivatized, and produced in regular sphere sizes.(26,27)

- **Selection of Chromatographic mode**

chromatographic modes determined by the subatomic weight and extremity of the analyte All contextual studies will focus on reversed-phase chromatography (RPC), the most extensively used method for small natural atoms. Ionizable mixtures (acids and bases) are routinely isolated by RPC using portable stages (to keep the analytes in non-ionized state) or ion-pairing reagents.(28)

- **Buffer selection**

Choice of buffer is governed by the pH that is desired. The pH range for reversed phase on silica-based packing is typically 2 to 8. It is important that the buffer has a pKa close to the desired pH since buffer controls pH best at their pKa. A general rule is to select a buffer with a pKa value of <2 units higher than the desired mobile phase pH.(29)

- **Buffer concentration**

For small molecules, a buffer concentration of 10-50 mM is usually sufficient. A buffer should not include more than 50% organic material. This will depend on the specific buffer as well as its concentration. The most frequent buffer systems for reversed-phase HPLC are phosphoric acid and its sodium or potassium salts. When testing organophosphate chemicals, sulfonate buffers can be used instead of phosphonate buffers.(30)

Selection of mobile phase

The ionogenic nature of the analyte and the hydrophobicity of the analytes in the mixture influence the selection of the mobile-phase and gradient conditions, respectively. Acidic analytes will remain unaltered in buffers with suitably low pH, improving retention. At higher pH, neutral basic chemicals are more maintained, while ionized acidic ones elute faster. Peak splitting can occur when the pKa of a chemical is similar to the pKa of the buffer and the analyte elutes as both a charged and uncharged species. The pH of a buffer has little impact on the retention of non-ionizable sample components. Acetonitrile (ACN), methanol (MeOH) and tetrahydrofuran (THF) are commonly used solvents in RP-HPLC having low UV cut-off of 190, 205 and 212nm respectively. These solvents are miscible with water. Mixture of acetonitrile and water is the best initial choice for the mobile phase during method development.(31,32)

Selection of detector

The detector is a very important component of HPLC. The chemical nature of the analysts, potential interference, detection limit required, availability and/or cost of detector all are depend on the selection of detector. The UV-Visible detector is a dual-wavelength absorbance detector for HPLC. This detector provides the high sensitivity necessary for routine UV-based applications such as impurity identification and quantification. Photodiode Array (PDA) Detector offers advanced optical detection for Waters analytical HPLC, preparative HPLC, or LC/MS system solutions. Its innovative software and optics provide great chromatographic and spectrum sensitivity. The Refractive Index (RI) Detector has great sensitivity, stability, and reproducibility, making it a suitable solution for analysing components with little or no UV absorption.(33)

Developing the approach for analysis

The initial stage in establishing an RP-HPLC analytical method is to choose various chromatographic parameters such as mobile phase, column, mobile phase flow rate, and mobile phase pH. All of these factors are determined through testing and then compared to the system suitability parameters. A retention duration of more than 5 minutes, a theoretical plate count of more than 2000, a tailing factor of less than 2, a resolution of more than 5, and a percent R.S.D. of the area of analyte peaks in standard chromatograms of no more than 2.0 percent are typical system suitability characteristics. When estimating two components simultaneously, the detection wavelength is typically an isosbestic point.(34)

Sample preparation

Sample preparation is critical in HPLC analysis because it ensures that the solution is repeatable and homogeneous enough to be put onto the column. The purpose of sample preparation is to establish a sample aliquot that is devoid of interferences, will not harm the column, and is compatible with the planned HPLC procedure, which implies that the sample solvent will dissolve in the mobile phase without impacting sample retention or resolution. Sample preparation begins with sample collection and ends with injection of the sample onto the HPLC column.(35)

Method optimization

Identify the "weaknesses" of the method and optimize the method through experimental design. Understand the method performance with different conditions, different instrument set ups and different samples.(36)

Method validation

The process of validating an analytical technique is the process by which laboratory tests verify that the method's performance characteristics fulfil the requirements for the intended analytical application. Any new or modified method must be validated to demonstrate that it is capable of producing consistent and reliable results when employed by various operators using the same equipment in the same or other laboratories. The type of validation programme required is entirely dependent on the specific method and its proposed applications.(37,38)

Components of method validation:

The following are typical analytical performance characteristics which may be tested during methods validation

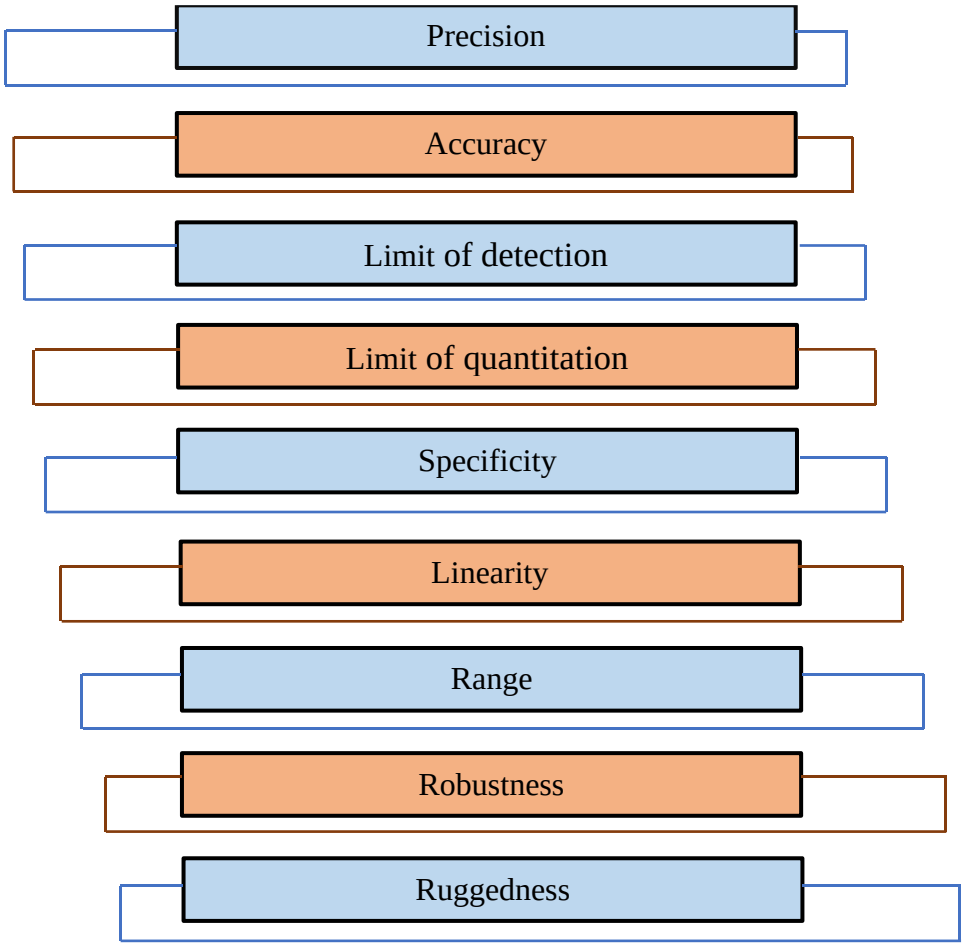

Fig. 4:- Validation parameters

Precision

The precision of an analytical procedure represents the nearness of agreement between a series of measurements got from multiple sampling of the same homogenous sample under the similar analytical conditions and it is divided into 3 categories.

- Repeatability: precision under same operating conditions, same analyst over a short period of time.
- Intermediate precision: method is tested on multiple days, instruments, analysts etc.
- Reproducibility: inter-laboratory studies.(39,40)

Accuracy

The accuracy of a measurement is defined as the closeness of the measured value to the true value. In a method with high accuracy, a sample (whose "true value" is known) is analyzed and the measured value is identical to the true value. Typically, accuracy is represented and determined by recovery studies. There are three ways to determine accuracy:

- Comparison to a reference standard.
- Recovery of the analyte spiked into blank matrix.
- Standard addition of the analyte.(41)

Limit of detection

The limit of detection is obtained by analyzing samples with known drug concentrations and determining the lowest level at which the analyte can be identified but not necessarily quantitated as an exact value. LOD is often expressed in terms of analyte concentration in the sample (ppm). The ICH recommends a number of ways for estimating the detection limit of a sample, based on the nature of the analyte, the applicability of the method, and the instrument used for analysis. Acceptable ways include signal-to-noise ratio, standard deviation of linearity plot slope, visual inspection, and response standard deviation.(42,43)

Limit of quantification

The quantification limit of an individual analytical process is the smallest amount of analyte in a sample that can be determined quantitatively with appropriate precision and accuracy. The quantitation limit is a quantitative test parameter for low amounts of chemicals in sample matrices, and it is widely used for determining impurities and/or degradation products.(44,45)

Specificity

It is the ability to measure the desired analyte in a complex mixture. It is the degree of bias caused by expected sample components and common interferences, determined by measuring the analyte with and without anticipated interferences.(46)

Linearity

The linearity of an analytical method is defined as the ability to obtain test results within a given range, which is directly proportional to the analyte concentration in the sample. Linearity is typically stated as the confidence limit around the regression line's slope. The ICH guidelines propose a minimum of five concentrations to establish linearity. The range of an analytical method is the range of analyte concentrations in a sample that have been shown to be determined with precision, accuracy, and linearity using the method.(47,48)

Range

The range of analytical method is the interval between the upper and lower levels of analytic that has been demonstrated to be determined with a suitable level of accuracy, precision, and linearity. The range is normally expressed in the same units as test results (e.g., percent, parts per million) obtained by the analytical method.(49)

Robustness

Robustness is defined as the measure of the ability of an analytical method to remain unaffected by small but deliberate variations in method parameters (e.g. pH, mobile phase composition, temperature and instrumental settings) and provides an indication of its reliability during normal usage. Determination of robustness is a systematic process of varying a parameter and measuring the effect on the method by monitoring system suitability and/or the analysis of samples.(50,51)

Ruggedness

Ruggedness is measure of reproducibility test results under the variation in conditions normally expected from laboratory to laboratory and from analyst to analyst. The Ruggedness of an analytical method is degree of reproducibility of test results obtained by the analysis of the same samples under a variety of conditions, such as; different laboratories, analysts, instruments, reagents, temperature, time etc.(52,53)

Quality by Design approach in Analytical Method Development

Dr. Joseph M. Juran first proposed the concept of Quality by Design (QbD) in several papers, claiming that quality may be planned. The concept of QbD was addressed in the ICH Q8 guidelines, which indicate that "quality should be built into the product by design, but quality cannot be tested in the product".(54,55) The acceptability of a drug material or a drug for its intended uses is referred to as quality. This term encompasses characteristics such as identity, purity, and strength. Quality by design is defined as "a systematic approach to development that begins with a predefined objective and emphasizes product and process understanding and process control, based on sound science and quality risk management" by ICH Q8 (R1).(56,57)

The main application of quality by design (QbD) principles for analytical method development is focused on the principle of building quality into the analytical method while it is being developed. As a result, the actual method development process for an analytical quality by design (QbD) method should be structured. The goal of QbD method development is to meet with predefined objectives. The goal of QbD method development can be demonstrated using HPLC as an example. The goal of the HPLC method for API is to separate and quantify the primary ingredient as well as the critical quality attributes (CQA) that may affect the drug product's quality. Specificity, linearity, accuracy, precision, robustness, and ruggedness should all be met by the specifications.(58,59)

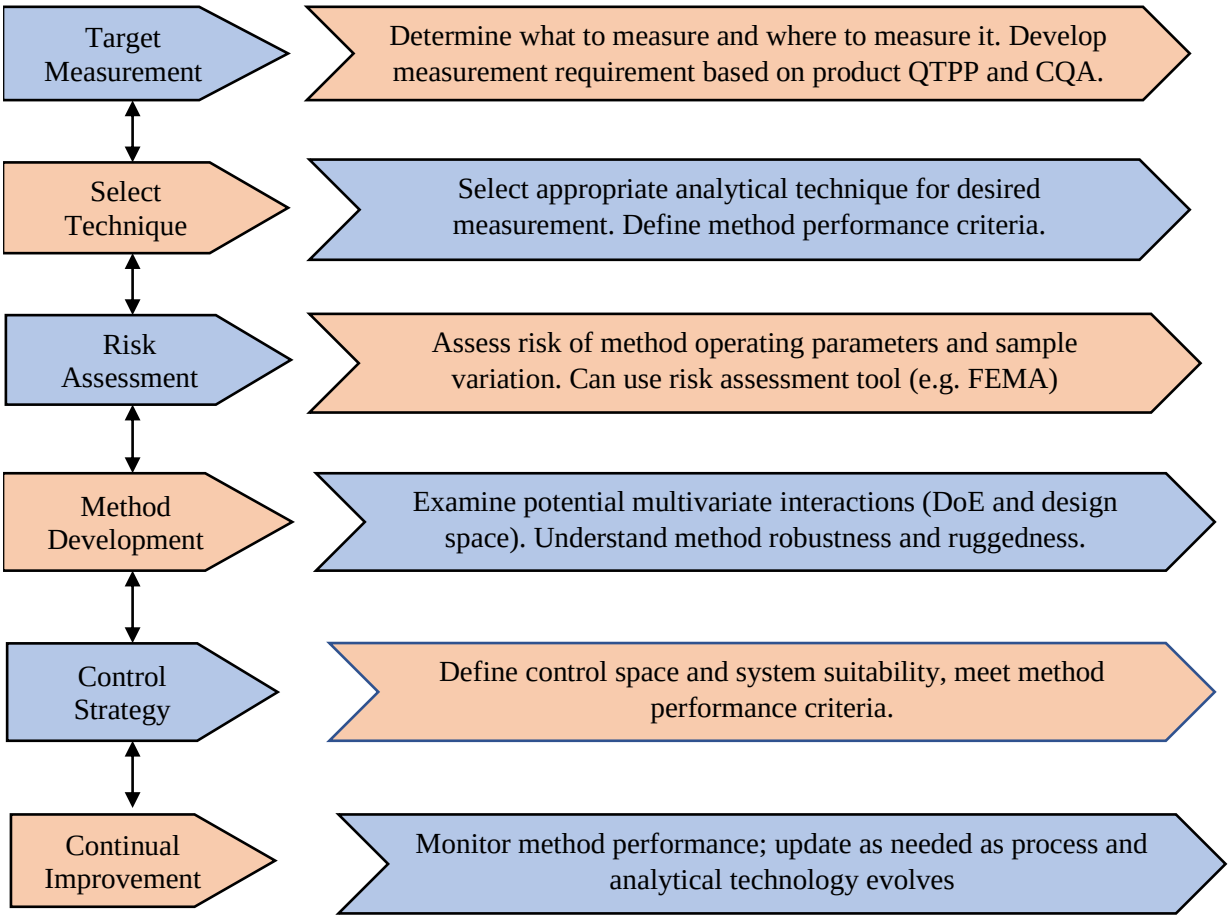

Fig. 5:- QbD approach for analytical method development

Method develops by QbD approach

Step 1: Defining method intent

Pharmaceutical QbD is a systematic practical strategy that begins with stated objectives and focuses on product and process understanding and control, therefore HPLC method development goals must be clearly defined. The analytical method's ultimate purpose is to separate and quantify the primary constituent.(60,61)

Step 2: Performing experimental design

A systematic experimental design is required for in-depth method knowledge and optimization. It creates a chromatographic database that will aid in method comprehension, optimization, and selection. Design of experiments (DOE) has frequently been used to optimize analytical procedures due to its application, such as a reduction in the total number of attempts that must be carried out, resulting in reduced reagent use and significantly lower laboratory tasks.(62)

Step 3: Evaluation of experimental results and selection of final method conditions:

The method's conditions must be reviewed using a three-tiered methodology. First, the conditions for peak symmetry, peak fronting, and peak tailing should be reviewed. Later, these conditions should be reviewed using more stringent criteria, such as tailing factor should be less than 1.5, etc.(63)

Step 4: Performing risk assessment with robustness and ruggedness evaluation

Once the final method is chosen based on method qualities, it is quite likely that the method will be reliable and operational throughout the product's lifetime. The fourth step of method development is primarily concerned with method verification and finalization, as well as the evaluation of method robustness and ruggedness. (64)

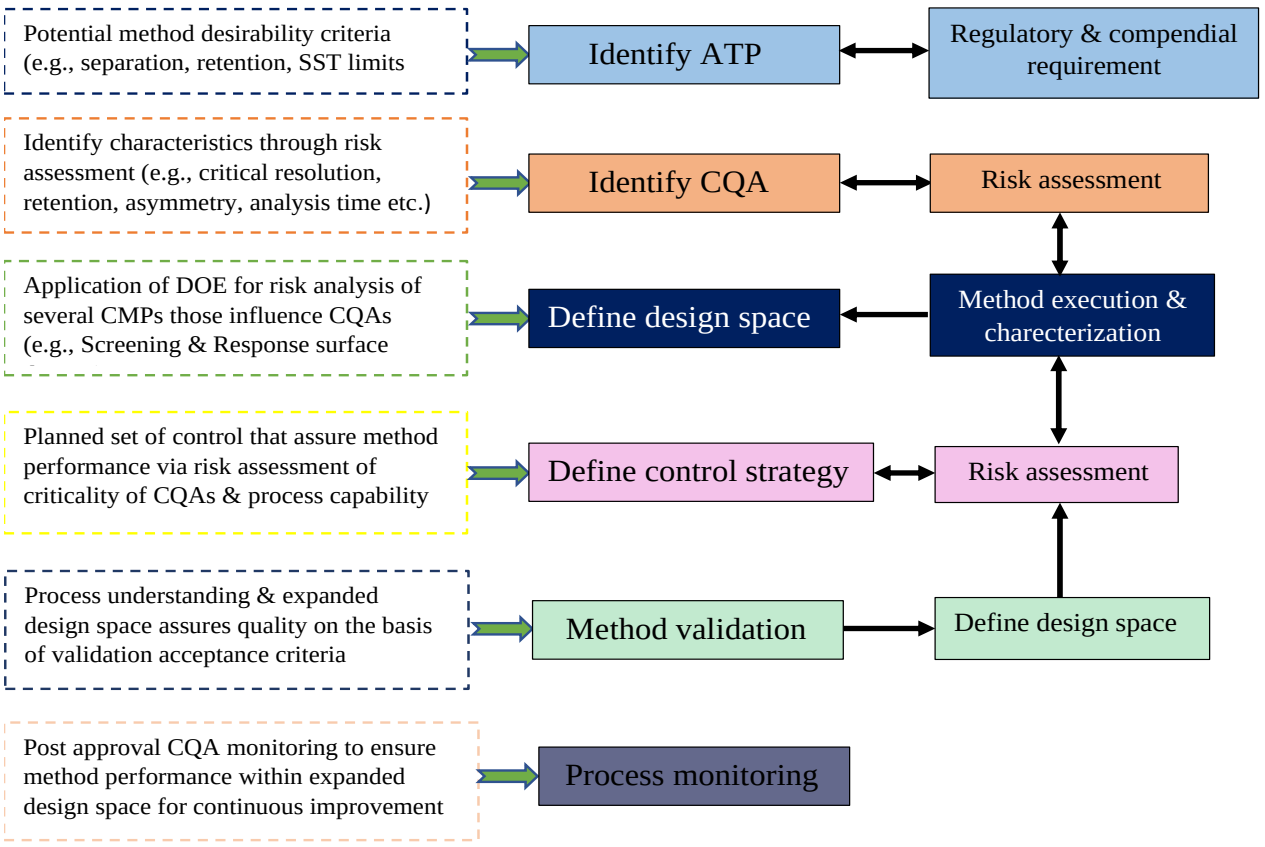

Fig. 6:- Key steps in QbD driven chromatographic method development

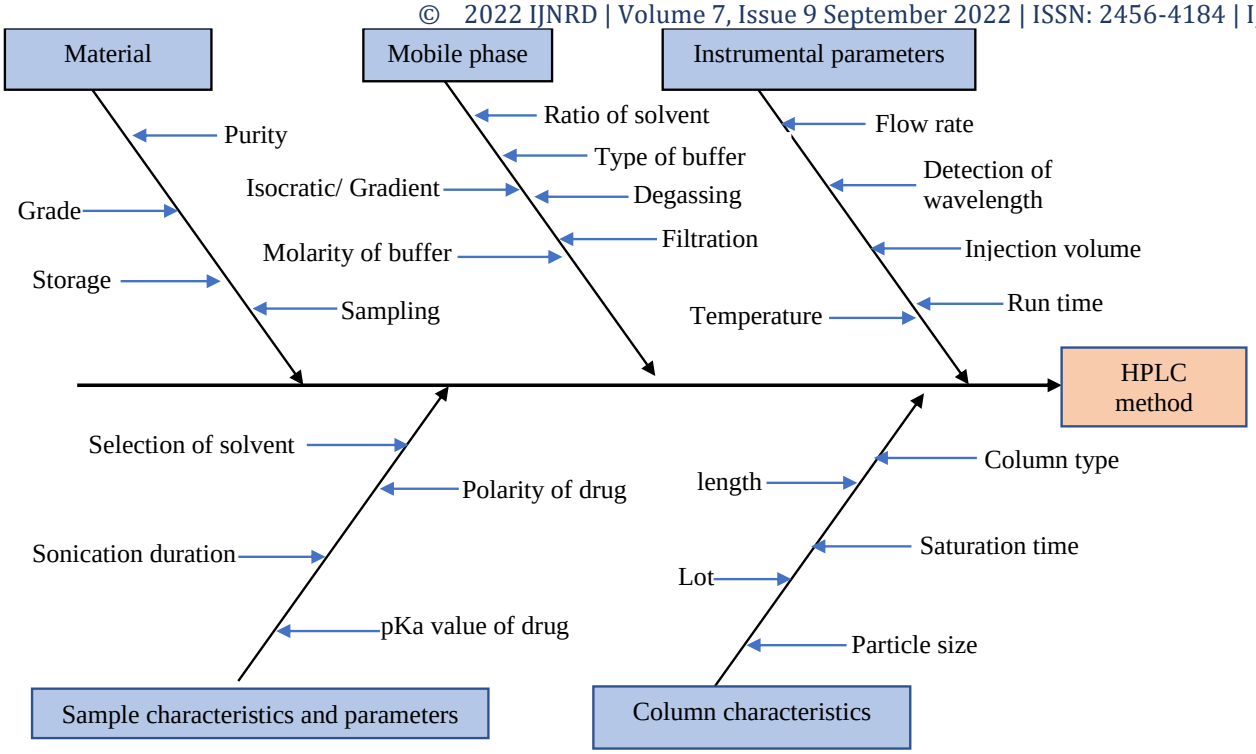

Fig. 7:- Experimental design in HPLC method development and validation

Analytical QbD method validation:

A QbD method validation approach is that the validation of analytical method over a range of different API batches. It uses both DoE and MODR knowledge for designing method validation for all kind of API manufacturing changes without revalidation. The approach provides the required ICH validation elements as well as information on interactions, measurement uncertainty, control strategy, and continuous improvement. This approach requires fewer resources than the traditional validation approach without compromising quality.(65,66)

Potential benefits of adopting QbD for analytical method

1. Scientific understanding of pharmaceutical process and method.
2. It provides a space for invention of new techniques by continuous improvement throughout life cycle.
3. Critical quality attributes are identified and their effect on final quality of product is analyzed.
4. It provides required design space for development.
5. Flexibility in analysis of API, impurities in dosage forms, stability samples, and metabolites in biological samples.
6. Reduction in variability in analytical attributes for improving the method robustness.
7. Minimize deviations and costly investigations.
8. Smooth process of method transfers to the production level.
9. It provides greater compliance with regulatory authorities.(67,68)

Conclusion

This article gives an idea that how to develop a method and how to validate it. The primary objectives of analytical method development and validation are identification, purification and eventually to qualification of any necessary drug etc. The development of analytical methods helps in understanding the critical parameters and to reduce effects on precision and accuracy. specific, linear, reliable, sensitive. The goal of a well-characterized method development effort is to develop a reliable method that can be demonstrated with a high degree of assurance to consistently produce data meeting predefined criteria when operated within defined boundaries. Analytical method development and validation by QbD plays a key role in the pharmaceutical industry for ensuring the product quality. The outcome of AQbD is the understanding from product development to commercial production.

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