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A Review: Analytical Method Development and Validation

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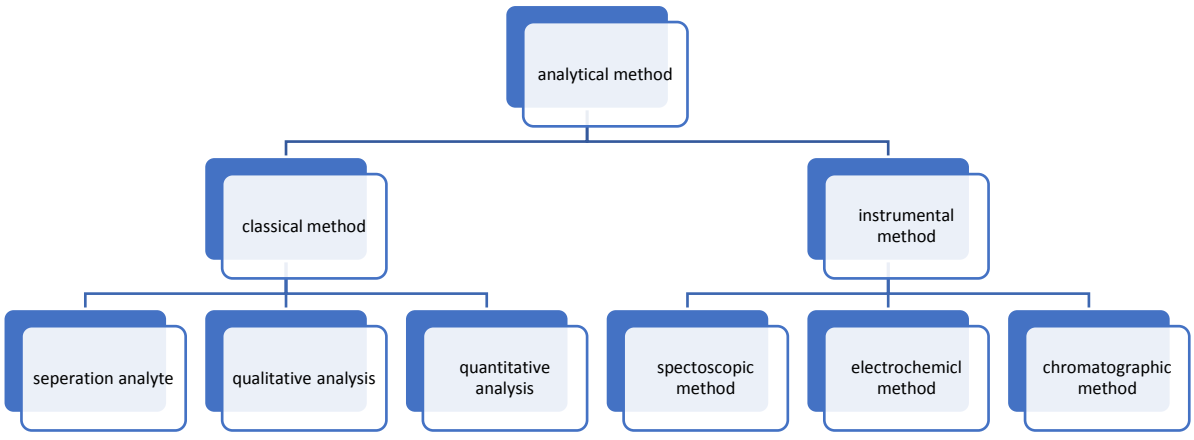
ABSTRACT
Quality assurance and quality control of pharmaceutical formulations and bulk pharmaceuticals both heavily rely on pharmaceutical analysis. The demand for novel analytical techniques in the pharmaceutical industries has increased due to the pharmaceutical industries' rapid expansion and the manufacture of drugs in different regions of the world. Development of analytical methods has therefore evolved into the core function of analysis. The improvement of analytical tools has led to recent developments in analytical methodologies. The development of better analytical methods and tools h
as resulted in shorter analysis times, greater precision and accuracy, and lower analysis costs. As a result, the majority of pharmaceutical companies are spending a significant amount of money to construct cutting-edge analytical laboratories.For active pharmaceutical ingredients (API), excipients, drug products, degradation products and associated compounds, residual solvents, etc., analytical procedures are developed and verified. As a result, it is now a crucial component of what the regulatory organisation requires. Official test methods are the end product of analytical technique development. In order to guarantee the identification, purity, safety, efficacy, and performance of drug goods, these techniques are utilised in quality control laboratories. Analytical techniques are becoming more important in manufacturing, according to regulatory agencies. The applicant must demonstrate control over the entire drug development process to regulatory authorities in order for their approval of the drug.
Key words: Validation, Quality Control, and Development of Analytical Methods.

ANALYTICAL METHODA: sample can be analysed qualitatively, quantitatively, or structurally for one or more analytes using an analytical method that uses a specific technique and comprehensive step-by-step instructions (Kissinger PT, 2002).

Figure 1: Classification of Analytical Methods



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I. INTRODUCTION

A subfield of chemistry known as analytical chemistry deals with the qualitative and quantitative identification of the constituent parts of substances, samples, and mixtures. There are two different kinds of analysis: qualitative analysis and quantitative analysis. The identification of mixture or sample's constituents or analytes is done by qualitative analysis. Quantitative analysis involves quantifying the components or analytes in a mixture or sample (Kenkel J, 2003). In addition to other disciplines like biology and zoology, as well as the arts like painting and sculpture, archaeology, space exploration, and clinical diagnostics, analytical data is needed in chemistry. Quality control in industrial industries, monitoring and controlling pollutants, clinical and biological studies, geological tests, fundamental and applied research are important areas of use for analytical chemistry (Kissinger PT, 2002).

Every year, more medications are being released onto the market. These medications could either be entirely new or structurally modified versions of already existing ones. A drug's introduction to the market and the date of its inclusion in pharmacopoeias frequently occur at different times. This is brought on by potential risks associated with long-term and widespread use of these medications, reports of novel toxicities (leading to their removal from the market), the emergence of patient resistance, and the launch of superior medications by rival companies. Standards and analytical techniques for certain medications may not be included in the pharmacopoeias under these circumstances. Therefore, the need to create newer analytical techniques for such medications arises. The following conditions are provided to the analyst by the method development in order for him to estimate the drug: the information needed to solve a certain analytical puzzle.

- The required sensitivity.
- The required accuracy.
- The required range of analysis.

The method validation / evaluation imply the process of documenting or providing that: analytical method provides analytical data for the intended use.

Validation analytical method require the following

- Assuring quality
- Achieving acceptance of products by the international agencies.
- Mandatory requirement purposes for accreditation as per ISO 17025 guidelines.
- Mandatory requirement for registration of any pharmaceutical product or pesticide formulation.
- Validation methods are only acceptable for under taking proficiency testing.
- This is brought on by potential risks associated with long-term and widespread use of these medications, reports of novel toxicities (leading to their removal from the market), the emergence of patient resistance, and the launch of superior medications by rival companies. Standards and analytical techniques for certain medications may not be included in the pharmacopoeias under these circumstances. It becomes necessary to develop newer analysis methods for such drugs as a result. The information required to complete a certain analytical puzzle is given to the analyst by the technique development so that he can estimate the drug under the following conditions. New analytical techniques must therefore be created for such medicines. The following are a few of the factors that led to the development of more modern drug analysis techniques (Mendham, 2001).

It's possible that no pharmacopoeias have approved the new medication or medication combination. A competent analytical method for the medicine may not have been reported in the literature due to patent laws. Excipients used in the formulation of the medicine may not be available as analytical procedures. methods for assessing a drug when it is mixed with other medicationsIt's possible that there are no analytical techniques for measuring the drug's concentration in bodily fluids. The current analytical processes could need pricey solvents and reagents. Additionally, it could need laborious extraction and separation techniques, which might not be trustworthy. The steps in developing a method are:

Documentation starts at the verybeginning of thedevelopment process. A system for full documentation of development studies must be established. All data relating to these studies must be recorded in laboratory notebook or an electronic database.

1. Analyte standard characterization

a) All known information about the analyte and its structure is collected i.e., physical and chemical properties.

b)The standard analyte (100 % purity) is obtained. Necessary arrangement is made for the

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proper storage (refrigerator, desiccators and freezer).
c) When multiple components are to be analysed in the sample matrix, thenumber of components is noted, data is assembled and the availability of standards foreach one is determined.
d)Only those methods (spectroscopic, MS, GC, HPLC etc.,) that are compatible with sample stability are considered.

2. Method requirements: The goals or requirements of the analytical method that need to be developed are considered and the analytical figures of merit are defined. The required detection limits, selectivity, linearity, range, accuracy and precision are defined.

3. Literature search and prior methodology: The literature for all types of information related to the analyte is surveyed. For synthesis, physical and chemical properties, solubility and relevant analytical Ravisankaret.al Indian Journal of Research in Pharmacy and Biotechnology ISSN: 2321-5674(Print) ISSN: 2320 – 3471(Online)
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4. Choosing a method:

Using the information in the literatures and prints, methodology is adapted. The methods are modified wherever necessary. Sometimes it is necessary to acquire additional instrumentation to reproduce, modify, improve or validate existing methods for in-house analytes and samples.
a) If there are no prior methods for the analyte in the literature, from analogy, the compounds that are similar in structure and chemical properties are investigated and are worked out. There is usually one compound for each analytical method already exist that is similar to the analyte of interest.

5. Instrumental setup and initial studies: The required instrumentation is to be setup. Installation, operational and performance qualification ofinstrumentation using laboratory standard operatingprocedures (SOP's) are verified. Always new consumables (e.g. solvents, filters and gases) are used.
For example, method development is never started on a HPLC column that has been used earlier. The analyte standard in a suitable injection / introduction solution and in known concentrations and solvents are prepared. It isimportant to start withan authentic, known standardrather thanwith a complex sample matrix. If the sample is extremely close to the standard (e.g., bulk drug), then it is possible to start work with the actual sample.

6. Optimization: Instead of utilising a trial-and-error method, during optimisation one parameter is modified at a time and a set of conditions is isolated. Every stage of the process is recorded (in a lab notebook) in case there are any dead ends. The work has been done according to an organised, logical approach.

7. Documentation of analytical figures of merit: The originally determined analytical figures of merit are limit of quantitation (LOQ), limit of detection(LOD), linearity, time per analysis, cost, sample preparation etc., are documented.

8. Evaluation of method development with actual samples: The sample solution should lead to unequivocal, absolute identification of the analyte peak of interest apart from all other matrix components.

9. Determination of percent recovery of actual sample and demonstration of quantitative sample analysis: Percent recovery of spiked, authentic standard analyte into a sample matrix that is shown to contain no analyte is determined.

UV-VIS spectroscopy: The amount of light absorbed at each wavelength in the UV and visible regions of the electromagnetic spectrum is measured in UV-visible spectroscopy. The visible (VIS, 400-800 nm) and ultraviolet (UV, 200-400 nm) areas of this absorption spectroscopy are used in electromagnetic radiations between 200 nm and 800 nm (Kumar S, 2006). The fundamental idea behind UV-visible spectroscopy is that various spectra are produced when ultraviolet or visible light is absorbed by a sample or chemical entity.When a molecule absorbs UV light, the electrons inside of it are excited, which causes the electrons to transition from a lower level to a higher electronic energy level. The reverse sort of transition results in the ultraviolet emission spectra. Water, methanol, ethanol, ether, chloroform, carbon tetrachloride, cyclohexane, and dichloroethane are the solvents

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used in UV spectroscopy the most frequently. The detection of functional groups, detection of conjugation, detection of geometric isomers, and detection of contaminants are all applications of UV spectroscopy (Chatwal GR and Anand SK, 2002).

HPLC method development: One of the most used analytical methods is high performance liquid chromatography (HPLC). HPLC is used to analyse more than 85% of generic medications. The original chromatography method was created in 1903 by Russian botanist M.S. Tswett, although it has undergone numerous modifications since then and is still in use today. The separation is accomplished by the interaction of the stationary phase and the mobile phase, which are the main components of the separation module in HPLC. The stationary phase and the mobile phase have opposite polarities and are equipped with high pressure pumps. A proper choice ofstationary phase and mobile phase is essential to reach desired separation. Ph of mobile phase, different types of buffer, column temperature, sample diluents, detection wavelength and many more are the variables which play a major role in method development.

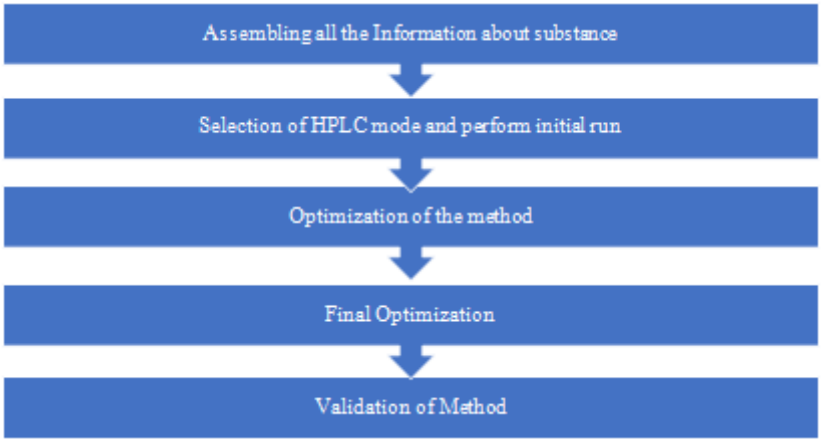
Choice of the Column: Column is the heart of HPLC system. Good silica and bonding process will provide the reproducible and symmetrical peak necessary for accurate qualification. Commonly used RP columns include C_{18} (USP L1), C_8 (USPL8), Phenyl (USP L11) and Cyno (USP L18). There is no good or bad column. They are chemically different boned phases and demonstrate significant changes in selectivity

Table.1. Types Column

Column	Phase	Solvent	Application
C18	Octadecyl	ACN	General, non polar
C8	Octyl	ACN	General, non polar
Phenyl	Styrl	ACN	Fatty acid
Diol	Dihydroxy hexyl	ACN	Protein
Amino	aminopropyl	ACN	Sugar, Anions

The method development process has no real beginning or end. Which "acceptable method performance" is being questioned? The goals established in this step determine the acceptable method performance. One of the most crucial factors is one that scientists frequently ignore. The many end points (i.e., expectations) will be covered in this section in decreasing order of importance.

Figure.2. Flowchart of method development



VALIDATION: Validation is a concept developed in the United States in 1978. The concept of validation has been broaden over the years to achieve many activities like from analytical methods used to control quality of drug substances and drug products up to computerized systems for clinical trials, process control or labelling. Validation is best seen as a necessary and prime part of cGMP. The word validation means evaluation of validity or the act of proving

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effectiveness. Validation is a team work involving people from different branches of plants. Method validation is a "process of establishing documented evidence" that provides a high level of guarantee that the product (equipment) will meet the requirements of the desired analytical applications (Lavanya G, et al., 2013).

Importance of validation:
• Assurance of quality
• Minimal batch failure
• Reduction in rejections
• Improved efficiency and productivity
• Increased output
• Reduced testing in process and in finished goods (Lavanya G, et al., 2013). Types of validation There are four types of validation:

1) Equipment validation a. Design Qualification b. Installation Qualification c. Operational Qualification d. Performance Qualification
2) Process validation a. Prospective validation b. Retrospective validation c. Concurrent validation d. Revalidation
3) Analytical method validation
4) Cleaning validation (Lavanya G, et al., 2013) Types of analytical procedures to be validated • Identification tests • Quantitative tests for impurities content • Limit tests for the control of impurities • Quantitative tests of the active moiety in samples of drug (Lavanya G, et al., 2013)
Steps in method validation
1) Develop a validation protocol, an operating procedure or a validation master plan for the validation.
2) Define the scope, purpose and applications of the method.
3) Define the performance parameters and its acceptance criteria.
4) Define validation experiments.
5) Verify related performance characteristics of equipment.
6) Qualify materials, ex. Standards and reagent.
7) Perform pre-validation experiments.
8) Adjust method parameters or/and acceptance criteria if required.
9) Perform full internal (and external) validation experiments.
10) Develop SOPs for implementing the method in the routine.
11) Define criteria for revalidation.
12) Define type and frequency of system suitability tests and/or Analytical Quality Control (AQC) checks for the routine.
13) Document validation experiments and results in the validation (Lavanya G, et al., 2013).
Parameters (components) of method validation
1) Accuracy
2) Precision
3) Linearity
4) Limit of detection
5) Limit of quantitation
6) Specificity
7) Range
8) Robustness

1) Accuracy: Accuracy is defined as the closeness of the test results to the true value.
2) Precision: Precision is defined as the measurement of closeness of agreement for multiple measurements on the same sample. The precision is expressed as the relative standard deviation. %RSD = Standard deviation/Mean ×100
3) Linearity: Linearity is the ability of analytical procedure to obtain a response that is directly proportional to concentration (amount) of analyte in the sample. Linearity is expressed as the confidence limit around the slope of the regression line.
4) Limit Of Detection (LOD): LOD is defined as lowest amount (concentration) of analyte in a sample that can be detected or identified, not quantified. LOD is expressed as a concentration at a specified signal: noise ratio, usually 3:1. LOD = 3.3 × S/ SD
5) Limit Of Quantitation (LOQ): LOQ is defined as lowest amount (concentration) of analyte is a sample that can be quantified. For LOQ, ICH has recommended a signal: noise ratio 10:1. LOQ = 10 × S/SD 6) Specificity: Specificity is defined as the ability of an analytical method to measure the analyte clearly in the presence of other components. This definition has following implications: a. Identification b. Purity tests c. Assay

II. CONCLUSION:

In order to demonstrate that a method is appropriate for its intended application, this article discusses how to build a method, what validation is, why it is important, the many types of validation, how to do the validation process, and its parameters. The main goals of developing analytical techniques are to identify, purify, and

ultimately qualify any required drugs, etc. The creation of analytical techniques aids in reducing the impact of crucial process parameters on precision and accuracy. In order to ensure that quality work is done in the process that supports the creation of medicines and products, validation is a vital approach in the pharmaceutical industry.

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