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A REVIEW ON DEVELOPMENT AND VALIDATION OF ANALYTICAL METHOD

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ABSTRACT

Analytical method development and validation play important role in discovery , development and manufacture of pharmaceuticals. Method development is the process of proving that an analytical method is acceptable for use to measure the concentration of an API in a specific compound dosage form which allow simplified procedure to be employed to verify that an analysis procedure , accurately and consistently will deliver a reliable measurement of an active ingradient in a compound preparation. The analytical method validation is essential for analytical method development and tested extensively for specificity, linearity, precision, range, and robustness.

KEY WORDS: Validation , Method Development, HPLC.

INTRODUCTION:[1-3]

The number of drug introduced into the market is increasing every year. These drug may be either new entities or partial structural modification of the existing one. Very often there is a time lag from the date of introduction of drug into market to the date of its inclusion in pharmacopeias. This happens because of the possible uncertainties in the continuous and wider usage of these drugs, reports of new toxicities development of patient resistance and introduction of better drug by competitors. Under these condition standard and analytical procedure for these drug may not be available in the pharmacopoeias. It becomes necessary, therefore to develop newer analytical method for such drugs.

ANALYTICAL METHOD DEVELOPMENT:[4-6]

Need

1. There may not be suitable method for the particular analyte in the specific sample matrix.
2. Existing methods may have error, artifact, and/ or contamination prone, or they may be unreliable (have poor accuracy, precision).
3. Existing methods may be too expensive, time consuming or energy intensive or they may not be easily automated.
4. Existing methods may not provide adequate sensitivity or selectivity in the samples of interest.
5. Newer instrumentations or techniques may have evolved that provide opportunities for improved methods, including improved analyte identification or detection limits, greater accuracy or precision or better return on investment.
6. There may be a need for an alternative method to confirm, for legal or scientific reasons, analytical data originally obtained by existing method.

Goal

1. Qualitative identification of specific analyte (s) of interest, providing some structural information to confirm ‘‘general behavior” (e.g. Retention time, color change, pH).
2. Quantitative determination, at trace level when necessary, that is accurate, precise and reproducible in any laboratory setting when performed according to established procedures.
3. Ease of use, ability to be automated, high sample throughput and rapid sample turnaround time.
4. Decreased cost per analysis from using simple quality assurance and quality control procedures.
5. Sample preparation that minimizes time, effort, material and volume of sample consumed.
6. Direct output of qualitative or quantitative data to laboratory computers in format usable for evaluation, interpretation, printing out and transmission to other locations via a network.

Method Development in HPLC :[7-9]

Before beginning of method development, we need to review what is known about the sample. The chemical composition of the sample can provide valuable clues for the best

choice of initial condition for an HPLC separation. Important information concerning sample composition and properties

1. Number of compounds present.
2. Chemical structures (functionality) of compounds.
3. Molecular weights of compounds.
4. Pk_a values of compounds.
5. UV spectra of compounds and maximum wavelength of absorbance.
6. Sample solubility.

Steps Involved in Development of HPLC Method

Literature Survey

Here a detailed account of all analytical methods developed for the drug is collected to avoid duplication of the method developed.

Chromatographic Mode

1. First reversed phase should be tried.
2. If not successful normal phase should be taken into consideration.
3. For ion exchange or ion pair chromatography, first ion suppression by pH control and reversed phase chromatography should be tried.

Selection of Stationary Phase

Column is referred to as the heart of HPLC separation process. Stable, high performance column is essential requisite for rugged and reproducible method. For high separation efficiency large number of theoretical plates are necessary per unit length of the column.

Selection of Mobile Phase

Reversed phase bonded packing, when used in conjunction with highly polar solvents; approach is ideal and is a universal system for liquid chromatography.

Mobile phase may be either single liquid or combination of liquids, which are compatible with sample, column and instrument.

Selection of Suitable Detector

Detector measures the compounds after their separation on the column. There are basically two types of detectors- the bulk property detectors and solute property detectors. UV detector is the first choice because of its convenience and applicability in case of most of the samples.

The latest version of equipments is available with photo diode- array detectors (PAD or DAD).

Analytical Method Validation:[10-12]

Successful acceptance of the validation parameter and performance criteria , by all parties involved ,requires the cooperative efforts of several departments, including analytical development ,QC, regulatory affairs and the individual requiring the analytical data. "Validation of analytical method is the process that establishes, by laboratory studies, that the performance characteristics of the method meet the requirements for the intended analytical applications." Typical analytical performance characteristics that should be considered in the validation of analytical methods are listed below

1. **Specificity**
2. **Accuracy**
3. **Precision**

1. Repeatability
2. Intermediate precision
3. Reproducibility
4. Linearity
5. Range
6. Robustness
7. Ruggedness
8. System Suitability Testing

Characteristics of Validation

Specificity

Specificity is the ability to assess unequivocally the analyte in the presence of components, which may be expected to be present. Typically these might include impurities, degradants, matrix etc.

Accuracy

The accuracy of an analytical procedure expresses the closeness of an agreement between the value, which is accepted either as a conventional true value or an accepted reference value and the value found. This is sometimes termed as trueness.

Precision

The precision of analytical procedure expresses closeness of agreement (degree of scatter) between a series of measurements obtained from multiple sampling of the same homogenous sample under prescribed conditions. It may be considered at three levels: It is expressed as standard deviation or coefficient of variation.

Repeatability

Repeatability expresses the precision under the same operating conditions over a small interval of time. Repeatability is also termed intra-assay precision.

Intermediate precision

Intermediate precision expresses within-laboratories variations: different days, different analyst, different equipment etc.

Reproducibility

Reproducibility expresses the precision between laboratories.

D. Linearity & Range

The linearity of an analytical procedure is the ability to obtain test results, which are directly proportional to the concentration of an analyte in the sample. The range of an 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 is of precision, accuracy and linearity

E.Robustness

The robustness of an analytical procedure is a measure of its capacity to remain unaffected by small, but deliberate variations in method parameters and provides an indication of its reliability during normal usage.

F. Ruggedness

The Ruggedness of an analytical procedure is the reproducibility of test result obtained by the analysis of the same sample under variety of condition, such as different laboratories , different analyst ,different instrument, different lots of reagent, different elapsed assay times , different assay temperature, different days etc.

G.System Suitability Testing

concept that the equipment , electronics , analytical operation , and samples to be analyzed constitute an integral system that can be evaluated as such.

When method should be validated?

A method should validated when it is necessary to verify that its performance characteristics are adequate for use for a particular analytical problem. For ex.

1. Method just developed
2. Revised method adapted to a new problem
3. When a established method is used in a different laboratories with different analyst or different equipment.
4. Demonstration of the equivalence between two method.

CONCLUSION

The efficient development and validation of analytical method are critical element in the development of pharmaceuticals. Success in these areas can be attributed to several important factors, which, in turn, will contribute to regulatory compliance. Experience is one of these factor both the experience level of the individual scientist and the collective experience level of the development and validation department. Improvement in analytical instrumentation leads to development of new technique like isocratic and RP-HPLC. Which evolved as the primary technique for the analysis of nonvolatile APIs and impurities?

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