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Review Article

METHOD VALIDATION OF COMPENDIAL ICP-OES METHOD FOR DRUG SUBSTANCES AS PER USP AND EU PHARMACOPOEIAS

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Method Validation is the main regulatory requirement in pharmaceutical analysis with compliance as per the guidelines or chapter any pharmacopoeia of the same scope. Method Validation is a critical quality attribute for the evaluation of any drug substance through an established method in the quality control laboratory. Validation is establishing documented evidences, which provides a high degree of assurance that a specific process will consistently produce a product meeting its predetermined specifications and quality characteristics. Validation is considered a good manufacturing practice (GMP) activity; validation experiments must be properly documented and performed on qualified and calibrated instrumentation and equipment. At this stage, there should be documented evidence that the method is robust. The USP has published specific guidelines for method validation for compound evaluation. USP defines eight steps for validation which are Accuracy, Precision, Specificity, Limit of detection, Limit of Quantitation, Linearity and range, Ruggedness, Robustness. This review was written to assist chemists/analysts to perform for method validation on ICP-OES. This review study may facilitate to academics and pharmaceutical industry personnel to know the analytical method validation of ICP-OES as per USP and EU guidelines.

Keywords: ICP-OES, QC Lab, Method Validation, USP, EU

INTRODUCTION

Elemental impurities include catalysts and environmental contaminants that may be present in drug substances, excipients, or drug products. These impurities may occur naturally, be added intentionally, or be introduced inadvertently (e.g., by interactions with processing equipment and the container closure system). When elemental impurities are known to be present, have been added, or have the potential for introduction, assurance of compliance to the specified levels is required.

Elemental impurities in pharmaceutical formulations can come from catalysts, formulation ingredients and process vessels. They can interfere with drug efficacy or elicit a direct toxic effect on the patient. For over 100 years regulators have demanded the testing of heavy metal impurities in pharmaceutical products. Elemental impurities analysis encompasses trace metal/heavy metal testing to evaluate pharmaceutical products for elevated concentrations of elements such as lead and arsenic that are of significant toxicological concern. In any product, impurities can delay development or can cause a recall of a product on the market.[1]

ICP-OES is a trace-level, elemental analysis technique that uses the emission spectra of a

sample to identify, and quantify the elements present. Samples are introduced into the plasma in a process that desolvates, ionises, and excites them.[2]

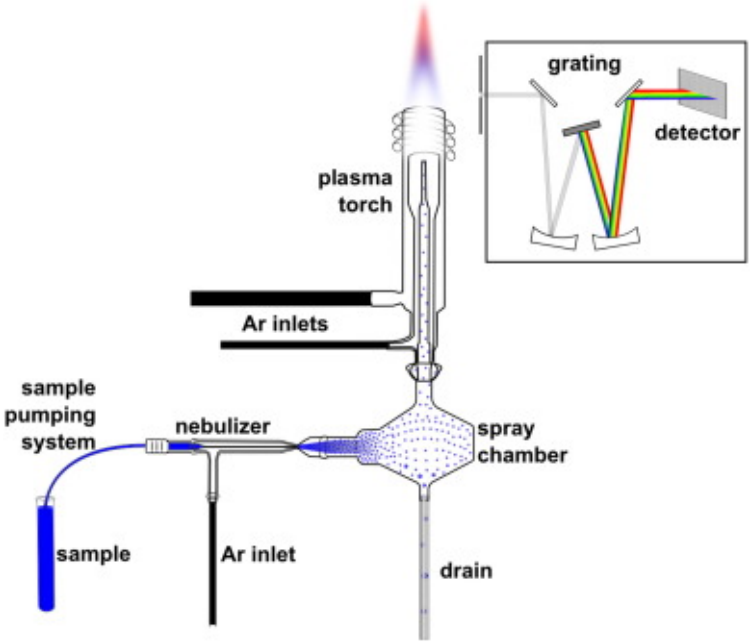

Figure no. 01 Schematic Diagram of ICP-OES

Analytical method Validation may be outlined as (ICH) "Establishing documented proof that provides a high degree of assurance that a particular activity can systematically produce a desired result or product meeting its preset specifications and quality characteristics.[3]

Specificity:[4]

EP –Specificity is the ability to ensure that the analytical procedures for sample preparation and measurement allow a reliable determination of the metals in the presence of components (e.g. carrier gas, impurities, and matrix) that may be expected to be present.

USP– The procedure must be able to unequivocally assess each Target element in the presence of components that may be expected to be present, including other Target elements, and matrix components.

Test Procedure:

The specificity of the elemental impurity method will be investigated by introducing the sample with spiked impurities to demonstrate the absence of interference with the elution of analyte.

Inject three replicates of sample solution with un-spiked impurities and three replicates of spiked sample solution.

Limit of Detection and Limit of Quantification:[4]

Limit of Detection:

EP: "Determination of limit of detection by the lowest concentration giving the signal clearly distinct from that obtained with a blank solution.

The detection limit of an individual analytical procedure is the lowest amount of analyte in a sample which can be detected but not necessarily quantities as an exact value"

USP: "The detection limit is a characteristic of limit tests. It is the lowest amount of analyte in a sample that stated experimental conditions. Thus, limit tests merely substantiate that the amount of analyte is above or below a certain level. The detection limit is usually expressed as the concentration of analyte (e.g., percentage, parts per billion) in the sample."

Limit of Quantification:

EP: "Determine the lowest concentration meeting the acceptance criterion. Use the results from the accuracy study. The Quantification limit of an individual analytical procedure is the lowest amount of analyte in a sample which can be quantitative determined with suitable precision and accuracy. The Quantification limit is a parameter of quantitative assays for low levels of compounds in sample matrices, and is used particularly for the determination of impurities and/or degradation products."

USP: "The limit of quantification is estimated by calculating the standard deviation of NLT 10 replicate measurements of a blank solution and multiplying by 10. When validating a procedure using the method of standard additions, the slope of standard applied to a solution of the test material is used. Other suitable approaches can be used.

A measurement of a test solution prepared from a representative sample matrix spiked at the estimated QL concentration must be performed to confirm accuracy. When validating a procedure using the method of standard additions, the validation criterion applies to the final experiment result, not the spike recovery of the individual standard addition levels."

The Limit of Quantification is established by Standard Deviation obtained from 10 replicates of blank using following formula.

LOQ = Standard Deviation × 10

Acceptance Criteria:

The determined LOD and LOQ of instrument by reading ten replicates of blank will be the acceptance limit of LOQ and LOD for Determination of Elemental Impurities by ICP-OES.

For the estimated limit of Quantitation to be considered valid, the measured concentration must be accurate and precise at a level 50% of the specification.

Accuracy/Recovery:[5]

EP – Recovery may be determined on a sample of the substance to be examined, spiked with a known quantity of a reference standard of the metal (3 concentration levels in the range of 50-150 per cent of the intended specification limit, even if the original concentration of the reference standard is at

the specified value), in triplicate.

USP - The Accuracy of an analytical procedure is the closeness of test results obtained by that procedure to the true value. The accuracy of an analytical procedure should be established across its range.

Test Procedure

Prepare individual sample of three different spiked concentrations over the range of 50%, 100% and 150%. Introduce 2 Unspiked samples and Spiked Sample with three different preparations spiked at each elemental impurity concentration. The recovery can be determined by the equation:

$$\text{Recovery (\%)} = \frac{\text{(Elemental impurity obtained – Elemental Impurity in Test sample)}}{\text{(Elemental Impurity added)}} \times 100$$

Acceptance Criteria:

The mean recovery will be within 70 to 150% of the theoretical value for non-regulated products. Recovery at each level, mean recovery and overall mean recovery should be 70 to 150.0%. Mean recovery and overall mean recovery should be between 70 to 150.0%.

Precision:[6]

Method Precision (Repeatability):

EP – Either 6 independent samples of the substance to be examined spiked with a suitable reference standard at the specified concentration level, or 3 concentration levels prepared in triplicate.

USP– The analytical procedure is assessed by measuring the concentration of six independently prepared sample solutions at 100 % of the test concentration.

Intermediate Precision (Ruggedness)

EP- The effect of random events (intra-laboratory variations) on the analytical precision of the method must be established. Acceptable experiments for establishing intermediate precision include performing the repeatability analysis on different days, or with different instrumentation, or by different analysts. Only 1 of the 2 experiment is required to demonstrate intermediate precision. It indicates intra-laboratory variations; different days, different analysts, different equipment.

USP- The effect of random events (intra-laboratory variations) on the analytical precision of the method must be established. Acceptable experiments for establishing intermediate precision include performing the repeatability analysis on different days, or with different instrumentation, or by different analysts. Only 1 of the 2 experiment is required to demonstrate intermediate precision. It indicates intra-laboratory variations; different days, different analysts, different equipment.

Test Procedure:

A. Method Precision - One sample solution containing the 100% target level of analyte will be prepared. Three replicates will be made from 6 different preparation of sample solution according to the final method procedure.

B. Intermediate precision - Intermediate precision (within-laboratory variation) will be demonstrated by two analysts, using one ICP-OES systems on different days. Inject the Calibration Standard preparation and Sample preparation for three replicates.

Acceptance Criteria:

A. For Method Precision, the RSD for the Elemental Impurity Obtained and Recovery percent of the impurity and should not be more than 20.0 % for the replicates of six preparations.

B. For Intermediate Precision, the Elemental impurities results obtained by two operators using two instruments on different days should have a statistical RSD NMT 25.0%.

Linearity:[7]

EP –The linearity of an analytical procedure is its ability (within a given range) to obtain test results which are directly proportional to the concentration (amount) of analyte in the sample.

USP – A response curve between the analyte concentration and intensity is prepared from NLT two standard solutions and a blank, at concentration that encompass the anticipated concentration of the test solution.

Range:[8]

EP – The range of an analytical procedure is the interval between the upper and lower concentration (amount) of analyte in the sample (including these concentrations) for which it has been demonstrated that the analytical procedure has a suitable level of precision, accuracy and linearity.

USP – The range of an analytical procedure is the interval between the upper and lower levels of analyte (including these levels) that have been demonstrated to be determined with a suitable level of precision, accuracy and linearity using the procedure as written. The range is normally expressed in the same units as test results (e.g., percent, PPM) obtained by the analytical procedure.

Test Procedure:

- Inject first and last level in six replicates and remaining all other levels in triplicates, adequately.
- Make sure to inject samples from the lowest concentration to the highest concentration to reduce the effects, if any, of carryover from the higher concentration samples.
- Calculate the % RSD at each concentration.
- Plot the analyte concentration for each set of dilutions separately versus the signal response (average of each set of injections).
- Perform linear regression analysis, but do not include the origin as a point made and do not force the line through the origin.
- Plot the sign and magnitude of the residuals versus analyte concentration.
- Check residual plot for outlying values and curvature.
- Evaluate y intercept to determine if there is

significant departure from zero.

Acceptance Criteria:

Linearity:

- Coefficient of determination (r^2) should be greater than 0.99
- There should be no curvature in the residuals plot.

Range:

- Coefficient of determination (r^2) should be greater than 0.99
- There should be no curvature in the residuals plot.

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Conflict of Interest

The authors declare that they have no conflict of interest