

⟨730⟩ PLASMA SPECTROCHEMISTRY

INTRODUCTION

Plasma-based instrumental techniques, which are useful for pharmaceutical analyses, fall into two major categories: those based on the inductively coupled plasma, and those where a plasma is generated at or near the surface of the sample. The inductively coupled plasma (ICP) is a high-temperature excitation source that desolvates, vaporizes, and atomizes aerosol samples and ionizes the resulting atoms. The excited analyte ions and atoms can then subsequently be detected by observing their emission lines, a method termed inductively coupled plasma–optical emission spectroscopy (ICP–OES; also referred to as inductively coupled plasma–atomic emission spectroscopy), or the excited or ground state ions can be determined by a technique known as inductively coupled plasma–mass spectrometry (ICP–MS). ICP–OES and ICP–MS may be used for either single- or multi-element analysis and used for either sequential or simultaneous analyses with good sensitivity over an extended linear range.

For additional information and discussion of the theory and principles of measurements, see *Plasma Spectrochemistry—Theory and Practice* (1730).

QUALIFICATION OF PLASMA SPECTROPHOTOMETERS

Qualification of the ICP–OES or the ICP–MS can be divided into three elements: installation qualification (IQ), operational qualification (OQ), and performance qualification (PQ)—see also the general chapter *Analytical Instrument Qualification* (1058).

Installation Qualification

The IQ requirements provide evidence that the hardware and software are properly installed in the desired location, and that the environment, in which the instrument will be used, is adequate.

Operational Qualification

The purpose of OQ is to demonstrate that instrument performance is suitable. In OQ, an instrument's performance is characterized using standards of known spectral properties to verify that the system operates within target specifications. OQ is a check of the key operational parameters performed after installation and after repairs and/or maintenance. Instrument vendors often have samples and test parameters available as part of the IQ/OQ package.

Performance Qualification

PQ determines whether the instrument is capable of meeting the user's requirements for all the parameters that may affect the quality of the measurement. Depending on typical use, the specifications for PQ may be different from the manufacturer's specifications. For validated methods, specific PQ tests, also known as system suitability tests, can be used in lieu of PQ requirements. A solution used in the initial standard curve of an ICP–OES or ICP–MS instrument must be reassayed as a check standard at appropriate, pre-established intervals throughout the analysis of the sample set.

For single-element ICP–OES analyses, when analytical wavelengths are between 200 and 500 nm, or concentrations are >1 µg/mL, the reassayed standard should agree with its expected value to within ±10%, or as specified in an individual monograph. For multi-element ICP–OES analyses, when analytical wavelengths are <200 nm or >500 nm, or at concentrations of <1 µg/mL, the reassayed standard should agree with its theoretical value to within ±20%, or as specified in an individual monograph. For single-element ICP–MS analyses, when analytical masses that are free of interferences and when concentrations are >1 ng/mL, the reassayed standard should agree with its expected value to within ±10%, or as specified in an individual monograph.

For multi-element ICP–MS analyses, or when concentrations are <1 ng/mL, or for single-element analyses where interferences may be present, the reassayed standard should agree with its expected value to within ±20%, or as specified in an individual monograph.

In cases where an individual monograph provides different guidance regarding the reassayed check standard for ICP–OES or ICP–MS, the requirements of the monograph take precedence. Specific procedures, acceptance criteria, and time intervals for characterizing ICP–OES or ICP–MS performance depend on the instrument and intended application.

PROCEDURE

Users must evaluate and select the type of material of construction, pretreatment, and cleaning of analytical labware used in ICP–OES and ICP–MS analyses. The material must be inert and, depending on the specific application, resistant to caustics, acids, and/or organic solvents. For some analyses, diligence must be exercised to prevent the adsorption of analytes onto the surface of a vessel; contamination of the sample solutions from metal and ions present in the container also can lead to inaccurate results. For the analysis of a ubiquitous element, it is often necessary to use the purist grade of reagent or solvent available. Check all solutions for elemental contamination before they are used in an analysis.

Standard Solution

Standard solutions are used to standardize the instrument at the time-of-use, and prepare these solutions as directed in the individual monograph. [NOTE—Commercially available single- or multi-element standard solutions, traceable to the National Institute of Standards and Technology or to an equivalent national metrology organization, can be used in the preparation of standard solutions.] Standard solutions, especially those used for ultra-trace analyses, may have limited shelf-life. Stability of standard solutions can vary depending on concentration, analyte of interest, storage container type, and storage conditions. For these reasons, standard solutions with concentrations <10 ppm (w/v) should be retained for NMT 24 h, unless stability is demonstrated experimentally.

The method of standard additions can be used for instrument standardization. This method involves adding a known concentration of the analyte element to the sample at NLT two concentration levels against an unspiked sample preparation. The instrument response is plotted against the concentration of the added analyte element, and a linear regression line is drawn through the data points. The absolute value of the x-intercept multiplied by any dilution factor is the concentration of the analyte in the sample, and many instruments will perform the analyte calculation automatically. Once a method has been developed and is in routine use, it is common practice to calibrate with a blank and a single standard. One-point standardizations are suitable for conducting limit tests on production materials and final products, provided that the methodology has been rigorously validated for sufficient specificity, sensitivity, linearity, accuracy, precision, ruggedness, and robustness.

Sample Solution

Although solid samples and slurried samples may be analyzed, it is generally necessary to prepare solutions of samples for analyses as directed in the individual monograph. Samples may be dissolved in any solvent, including organic solvents or acids/bases, that are compatible with the instrument system. Samples that are not soluble in a solvent require digestion. A variety of digestion techniques could be used to dissolve a sample. These include hot-plate and microwave-assisted digestions, including open-vessel and closed-vessel approaches. Note that open-vessel digestion generally is not recommended for the analysis of volatile metals, e.g., selenium and mercury.

Analysis

The instrument must be standardized for quantitation at the time of use, following the procedure as directed in the individual monograph for the instrumental parameters. The response of standard solutions that bracket the target concentration of an analyte in a sample is determined against an appropriate blank. The detector response is plotted as a function of the analyte concentration. When an analysis is performed at or near the detection limit, the analyst cannot always use a bracketing standard. In such a case, a standard prepared at or near (within $\pm 10\%$ of) the detection limit should be run in triplicate, with an acceptance criteria of $\pm 10\%$ of the theoretical value for the standard for single-element standards, and $\pm 20\%$ of the theoretical value for the standard for multi-element standards.

To demonstrate the stability of the system's initial standardization, the analyst must reassay a solution used in the initial standard curve as a check standard at appropriate, pre-established intervals throughout the analysis of the sample set. Unless otherwise indicated in the individual monograph, the reassayed standard should meet the same acceptance criteria as those outlined in the PQ section above. Sample concentrations are calculated versus the working curve generated by plotting the detector response versus the concentration of the analyte in the standard solutions, and most instruments perform this calculation automatically.

VALIDATION AND VERIFICATION

Validation

Validation is required when the ICP–OES or ICP–MS method is intended for use as an alternative to the official procedure for testing an official article. The objective of the ICP–OES or the ICP–MS procedure validation is to demonstrate that the measurement is suitable for its intended purpose, including quantitative determination of the main component in a drug substance or a drug product (Category I assays), quantitative determination of impurities or limit tests (Category II), and identification tests (Category IV). [NOTE—For definition of different categories, see *Validation of Compendial Procedures* (1225).] Depending on the category of the test, analytical procedure validation for the ICP–OES or ICP–MS requires the testing of linearity, range, accuracy, specificity, precision, detection limit, quantitation limit, and robustness. These analytical performance characteristics apply to externally standardized methods and to the method of standard additions.

General chapter (1225) provides definitions and general guidance on the procedures for analytical validation without indicating specific validation criteria for each characteristic. The intention of the following sections is to provide the user with specific validation criteria that represent the minimum expectations for this technology.

ACCURACY

For Category I assays or Category II tests, accuracy can be determined by conducting recovery studies with the appropriate matrix spiked with known concentrations of elements. It is also an acceptable practice to compare assay results obtained using the ICP–OES or ICP–MS procedure under validation to those of an established analytical procedure. In standard addition methods, accuracy assessments are based on the final intercept concentration, not the recovery calculated from the individual standard additions.

Validation criteria: 95.0%–105.0% mean recovery for the assay, and 70.0%–150.0% mean recovery for the impurity analysis. These criteria apply throughout the intended range.

Precision

REPEATABILITY

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

Validation criteria: The relative standard deviation is NMT 5.0% for the drug substance assay, NMT 5.0% for the drug product assay, and NMT 20% for the impurity analysis.

INTERMEDIATE PRECISION

The effect of random events on the analytical precision of the procedure should be established. Typical variables include performing the analysis on different days, using different instrumentation, or having the method performed by two or more analysts. As a minimum, any combination of these factors totaling three experiments will provide an estimation of intermediate precision. For example, this could be one analyst on each of 3 days, or one analyst on two sets of equipment on two different days for one instrument; three analysts could be on the same piece of equipment.

Validation criteria: The relative standard deviation is NMT 8.0% for the drug substance assay, NMT 8.0% for the drug product assay, and NMT 25.0% for the impurity analysis.

SPECIFICITY

The procedure must be able to unequivocally assess each analyte element in the presence of components that are expected to be present, including any matrix components.

Validation criteria: Demonstrated by meeting the accuracy requirement

QUANTITATION LIMIT

The limit of quantitation (QL) 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 standards applied to a solution of the test material is used. Other suitable approaches can be used (see (1225)).

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 experimental result, not the spike recovery of the individual standard addition levels.

Validation criteria: The analytical procedure should be capable of determining the analyte precisely and accurately at a level equivalent to 50% of the specification.

LINEARITY

A response curve between the analyte concentration and absorbance is prepared from NLT two standard solutions and a blank (for a total of three data points), at concentrations that encompass the anticipated concentration of the test solution. The standard curve is then evaluated using appropriate statistical methods, such as a least-squares regression.

For experiments that do not yield a linear relationship between analyte concentration and the ICP–OES or ICP–MS response, appropriate statistical methods must be applied to describe the analytical response.

Validation criteria: Correlation coefficient (*R*), NLT 0.995 for Category I assays and NLT 0.99 for Category II quantitative tests

RANGE

Range is the interval between the upper and lower concentrations (amounts) 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 that is demonstrated by meeting the precision, accuracy, and linearity requirements.

Validation criteria: For Category I tests, the validation range for 100.0% centered acceptance criteria is 80.0%–120.0%. For noncentered acceptance criteria, the validation range is 10.0% below the lower limit to 10.0% above the upper limit. For content uniformity, the validation range is 70.0%–130.0%. For Category II tests, the validation range covers 70.0%–130.0% of the acceptance criteria.

ROBUSTNESS

The reliability of an analytical measurement is demonstrated by deliberate changes to experimental parameters. Because certain changes to experimental parameters could result in potential safety issues or damage to equipment, robustness is demonstrated by meeting the intermediate precision requirements set forth above.

Verification

U.S. Current Good Manufacturing Practices regulations [21 CFR 211.194(a)(2)] indicate that users of the analytical procedures, as described in *USP–NF*, are not required to validate these procedures if they are provided in a monograph. Instead, users must simply verify their suitability under actual conditions of use.

The objective of ICP–OES or ICP–MS procedure verification is to demonstrate that the procedure, as prescribed in a specific monograph, should be executed by the user with suitable accuracy, specificity, and precision using the instruments, analysts, and sample matrices available. According to *Verification of Compendial Procedures* (1226), if the verification of the compendial procedure by following the monograph is not successful, the procedure may not be suitable for use with the article under test. It may be necessary to develop and validate an alternative procedure as allowed in *General Notices*, 6.30 *Alternative and Harmonized Methods and Procedures*.

Verification of compendial ICP–OES or ICP–MS methods should, at a minimum, include the execution of the validation parameters for specificity, accuracy, precision, linearity, and limit of quantitation, when appropriate, as indicated in *Validation*.

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