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Review Article

A Basic Strategic Approach for Method Development by Inductively Coupled Plasma Mass Spectrometry (ICP-MS): A Review

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ABSTRACT

Method development for ICP-MS entails optimizing parameters to ensure precise and accurate elemental measurements. Sample preparation involves selecting techniques like digestion and dilution. Instrument setup optimizes plasma power and calibration with certified reference materials. Mass selection considers sensitivity and interference. Background correction methods account for spectral interferences. Internal standards correct for variations. Quality control ensures accuracy through replicate analyses and spike recoveries. Data analysis involves quantification and validation based on regulatory guidelines. Method optimization refines parameters for improved sensitivity and robustness. Comprehensive documentation and SOPs maintain consistency. Validation assesses accuracy, precision, and linearity according to standards like USP and ICH. Overall, this systematic approach guarantees reliable elemental analysis using ICP-MS.

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Introduction

ICP-MS, short for inductively coupled plasma mass spectrometry, utilizes to ionize samples [1-3]. This technique enables the sensitive detection of elemental impurities even at trace levels, with an instrument detection limit typically below 1 ppt [4-7]. The remarkable sensitivity of ICP-MS, along with its exceptional measurement specificity and capability to analyze multiple elements simultaneously, positions it as the preferred choice for pharmaceutical companies aiming to comply with new elemental impurities regulations set by USP [8-11]. ICP-MS is one of the two spectroscopic techniques specified within the General Chapter USP <233> for determining elemental impurities present in pharmaceuticals [12,13].

Principles of operation

The nebulizer, spray chamber, plasma torch, and detector are among the common components shared by all ICP-MS designs that are now in use [14,15]. The designs of the vacuum chamber, mass separation device, ion focusing system, and interface, however, might vary greatly. In the chapters that follow, specific descriptions of the instrument hardware will be given. The ICP-MS's operating principles are concerned. An ICP-MS system's basic parts are displayed in Figure 1. In this configuration, it is typical to use a peristaltic pump for transferring the sample, which is normally in liquid form, into a nebulizer at a rate of 1 mL/min. Here, argon gas is added at a rate of around 1 L/min to transform it into a fine aerosol [16-19].

Basic key points for a developing method

Sample preparation

Choice of reagent and standard

External standardization

Standard additions

Addition calibration

Internal standardization

Interferences

Sample preparation

As previously mentioned, ICP-MS was initially developed for analyzing liquid samples. When dealing with non-liquid samples, some form of sample preparation is necessary to dissolve them [20,21].

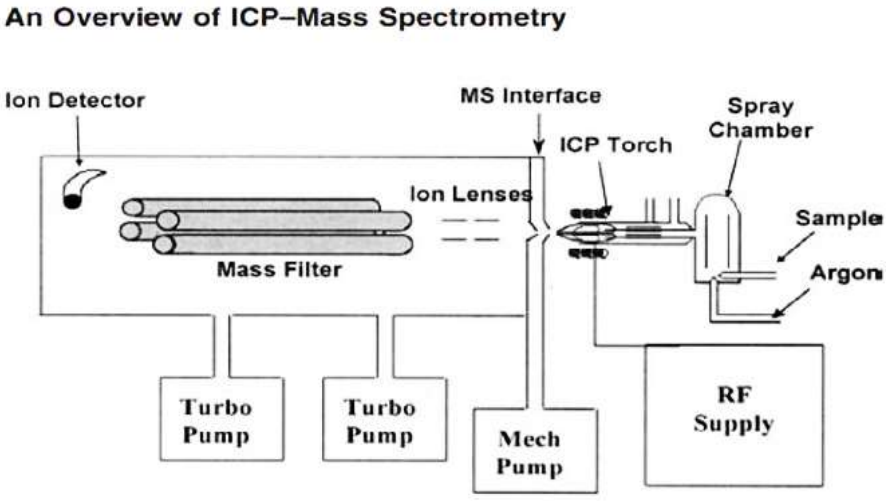

Figure 1: Basic instrumental components of an ICP mass spectrometer

This step is crucial in the overall ICP-MS analytical process due to the potential for contamination during grinding, sieving, weighing, dissolving, and diluting the sample. Sample dissolution methods play a vital role in sample preparation, as described below [14,16].

Sample dissolution methods

(1) Using concentrated acids and oxidising agents such as nitric acid (HNO_3), perchloric acid ($HClO_4$), hydrofluoric acid, aqua regia, hydrogen peroxide, or mixtures of these, hot plate, pressure bombs, or microwave digestion. These techniques are frequently used for biological samples, minerals, soils, sediments, and metals.
(2) Dissolution using strong bases, such as trimethyl ammonium hydroxide (TMAH) or caustic, which is usually applied to biological materials.
(3) Heating in a metal crucible (such as platinum, silver, or nickel) with fusion mixes or fluxes like lithium metaborate, sodium carbonate, or sodium peroxide, and then re-dissolving in a diluted mineral acid. This method is usually used for ceramics, ores, rocks, slags, and hard-to-mine minerals.
(4) Use a heated muffle furnace, heat lamp or flame for dry ashing, and then dissolve the residue in diluted mineral acid once again. This technique is frequently applied to biological or organic matrices.
(5) Wet ashing is commonly used for organic, petrochemical, and biological samples. It entails the use of strong acids along with heat.
(6) Organic solvent dissolution, which is usually applied to samples that are oil- or organic-based.
(7) Selecting the appropriate one can be highly complex and contingent on various factors, including sample size [22,23].

Reagents and standards

Consideration must be taken while choosing reagents, especially when aiming for sub-parts-per-trillion (sub-ppt) concentration levels, to ensure that both their choice and purity are adequate. These days, a lot of producers of laboratory chemicals provide ultra-high purity grades of compounds, acids, and fusion combinations that are especially designed to work with ICP-MS. Therefore, when preparing and diluting samples, it is essential to use the finest quality chemicals and water. In ICP-MS, the quality of the deionized water used for cleaning and dilution of containers and vessels is very important. Reagent blank levels are influenced by contaminants, which may have an effect on instrument performance and technique detection limits. Therefore, it is crucial to use the purest chemically pure water while doing ICP-MS investigations. There are several techniques for purifying water that remove organic matter, particles, and trace metals by combining filters, ion exchange cartridges, and/or reverse osmosis systems. The water produced by these ultra-high-purity water systems, which are similar to those used in semiconductor fabrication, usually has a resistance more than 18 Megohms.
The choice of calibration standards raises further concerns. It might be counterproductive to use calibration standards made for a single-element method like atomic absorption (AA), as ICP-MS can quantify more than 70 distinct elements [13,16,24]. Only the analyte element is verified for these single-element standards; no other elements are. As a result, using calibration standards designed especially for a multi-element method like ICP-MS is crucial. It does not matter if the standards are single- or multi-element; what matters is that the certificate contains details on the suite of analyte elements of interest and any possible interferents. In addition, it is ideal if the certified values can be traced back to national institute of standards and technology (NIST) reference materials and have been verified using both traditional wet procedures and instrumental techniques. Moreover, understanding the shelf life of these standards and chemicals, as well as the effects of long-term storage on the concentration of analyte elements, particularly at such low levels, is important [25].

External standardization

This process involves first measuring a blank solution, followed by a series of standard solutions to construct a calibration curve across the expected concentration range. Typically, a blank and up to three standards with varying analyte concentrations are analyzed. Increasing

the number of points on the calibration curve by adding more standards may enhance accuracy, especially when the calibration range is extensive. However, it is rarely necessary to utilize more than five standards for calibration. After measuring the standards, unknown samples are analyzed, and their analyte intensities are compared against the calibration curve. During prolonged analysis periods, it is common practice to update the calibration curve either by recalibrating the instrument with a full set of standards or by analyzing a single midpoint standard. The following protocol outlines a typical calibration using external standardization: 1) blank>, 2) std. 1>, 3) std. 2>, 4) std. 3>, 5) sample 1>, 6) sample 2>, 7) sample n, 8) recalibrate, 9) sample n+1, *etc*. [24]. It is important to highlight that while the graph in Figure 2 illustrates a calibration for a single element, ICP-MS is commonly employed for analyzing multiple elements simultaneously. Therefore, multi-element standards are typically utilized to generate calibration data. It is imperative to utilize multi-element standards specifically designed for ICP-MS to ensure accurate results. Single-element atomic absorption standards are not appropriate for this purpose, as they are certified only for the target element and not for others [24,26]. Consequently, their purity cannot be guaranteed for other elements, rendering them unsuitable for creating multi-element standards for use with ICP-MS. Similarly, multi-element standards for ICP-OES are not recommended, as they are certified for a group of elements and may contain other elements at higher concentrations, which could impact the multi-element calibration for ICP-MS [27-30].

Standard additions

By spiking samples with known analyte concentrations, this calibration method offers an efficient means of reducing sample-specific matrix effects [1,2]. Measurement of a blank solution's intensity comes first in standard addition calibration. After that, known concentrations of each element to be determined are "spiked" into the sample solution. For every element that has a spike applied, the device generates a calibration curve by measuring the response for the spiked samples. Plotting each spiking element's intensity after subtracting a blank against its concentration value creates the calibration curve. The un-spiked sample solutions are examined and contrasted with the calibration curve subsequent to the creation of the calibration curve.

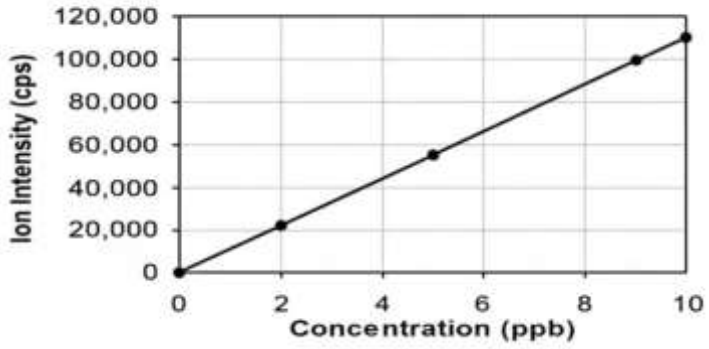

Figure 2: A simple linear regression calibration curve

The instrument software calculates the un-spiked concentration of the analytes in the unknown samples based on the slope of the calibration curve and the location of its x-axis intercept.

Figure 3 illustrates this by showing both the sample intensity calibration and the sample spiked with 2 and 5 ppb of the analyte. Where the calibration line crosses the x-axis' negative side indicates the sample's concentration. A typical calibration utilising the method of

standard additions is summarised in the process that follows. 1. Blank 2. Sample 1 that was spiked (spike conc. 1)> 3. Sample 1 that was spiked (spike conc. 2) 4. First un-spiked sample 5. Blank> 6, sample 2 (spike conc. 1) that was spiked 7. Sample 2 (spike conc. 2) that was spiked 8. Sample 2 was without spikes [24,26].

Addition calibration

Unfortunately, using the standard addition approach requires that all of the analytes of interest be spiked into each sample, which may be somewhat labor consuming, especially when analyzing a large number of samples. Thus, in ICP-MS, a modified variant called "addition calibration" is more frequently used. On the other hand, this method works only if every sample has a similar matrix. The initial (or typical) sample is the only one that is enriched with known analyte concentrations; otherwise, it functions similarly to standard adds, and then assuming that every sample has a matrix similar to the first one, the remaining sample batch is examined in comparison to this calibration. The following protocol summarizes a typical calibration using the method of addition calibration. 1. Blank> 2. spiked sample 1 (spike cont. 1)> 3. spiked sample 1 (spike cont. 2)> 4. Un-spiked sample 1> 5. Un-spiked sample 2> 6. Un-spiked sample 3> 7, *etc*. [24, 27-30].

Internal standardization

The implementation of internal standardization varies depending on the analytical technique being utilized. In quantitative analysis, internal standard elements are chosen based on their similar ionization characteristics to the analyte elements. Each internal standard is bracketed with a group of analytes, with the software assuming that elements within a group are similarly affected by the matrix. Changes in the ratios of internal standard intensities are then used to correct analyte concentrations in the unknown samples.

An further popular standardisation technique used in ICP-MS is called "internal standardisation." Internal standardisation, in contrast to absolute calibration approaches, is used to take into consideration differences in analyte sensitivity resulting from variations in the concentration and composition of matrix components within the sample.

A non-analyte isotope that is introduced to the blank solution, standards, and samples before analysis is referred to as an internal standard. To cover the analyte components of interest in the samples, three or four internal standard elements are often introduced.

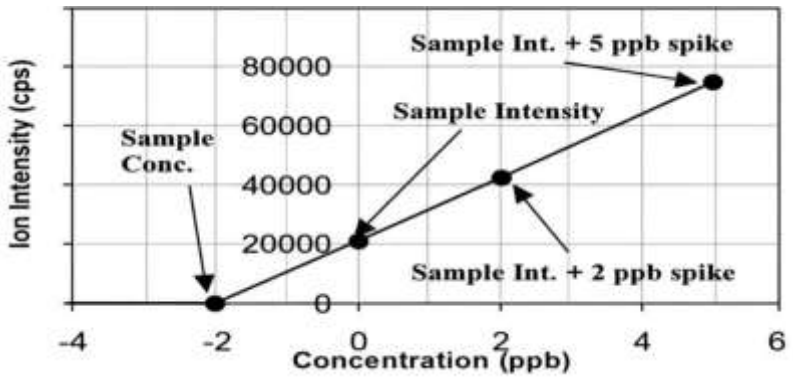

Figure 3: A typical ‘‘method of additions’’ calibration curve

By comparing the intensity values of the internal standard in the unknown samples to those in the calibration standards, the programme modifies the analyte concentration in the unknown samples [14].

For semi-quantitative analysis employing a stored response table, the purpose of the internal standard is similar but implemented slightly differently. Throughout a predetermined mass range, instrument drift or

matrix-induced suppression are continually corrected for using a semi-quantitative internal standard. When utilizing a single internal standard, the intensity of the internal standard determines how much each selected mass for determination is updated by. The programme interpolates intensity values depending on the mass difference between the analyte and the closest internal standard element if numerous internal standards are utilised, which is advised for measurements across a large mass range of masses. Remarkably, the majority of instruments have the ability to report raw data in the event that a calibration graph comparison is not requested. This enables viewing of the raw data file prior to reprocessing, selective use of ICP-MS data-processing techniques, and analysis using external data-processing procedures. The availability of raw data is mainly meant for nonroutine applications, like time-resolved transient peaks produced by laser sampling devices and chromatography separation techniques, or for users who need to process data using algorithms other than those offered by the instrument software [14,31].

Interferences

Interferences in ICP-MS are generally classified into three major groups— spectral-, matrix-, and physical-based interferences (Figure 4) [15].

Spectral interferences

interference, resulting from the combination of two or more atomic ions. These interferences arise from several sources, usually related to the nebulizer or plasma gas used, matrix components in the sample or solvent, additional elements in the sample, or oxygen/nitrogen entrained from the surrounding air. Spectral overlaps, for example, are frequently observed

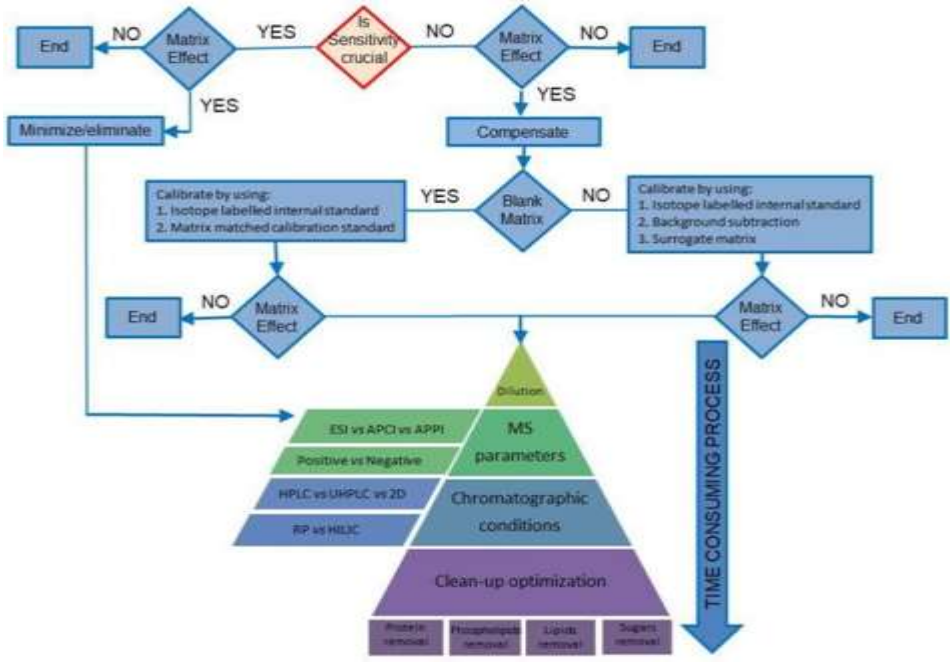

Figure 4: Ways to compensate for matrix interferences

in the argon plasma due to the mixing of argon ions with other species. Interestingly, at mass 40, the most common isotope of calcium is strongly interfered with by the most frequent isotope of argon [32-40]. Similarly, the combination of argon and oxygen in an aqueous sample generates the 40Ar16O+ interference, exerting a notable influence on the principal isotope of iron at mass 56 [40-46].

Ways to compensate for spectral interferences

Now let's examine the various methods for minimizing spectral interferences. Removing the

matrix in some form was one of the earliest methods used to overcome significant spectrum interferences produced from matrices. This was done in the past by using a complexing agent to precipitate the matrix and then filtering out the precipitate. But more recently automated matrix removal/analyte preconcentration methods employing apparatus similar to that used in chromatography have been used to do this. In fact, because to the matrix and spectrum issues brought on by such high quantities of sodium and magnesium chloride, this is the recommended technique for determining trace metals in seawater.

(1) Cool/Cold Plasma Technology

(2) Collision/Reaction Cells

(3) High-Resolution Mass Analyzers

Matrix interferences

(1) Matrix Effect occur when elements in the sample matrix change:

Size of the droplets produced by the nebulizer

Efficiency of ionization in the plasma

(2) Matrix Effect cause the slope of the analytical calibration curve to change

Caused by change in analyte or internal standard signal

(3) ICP-MS Matrix Effect can occur with > 50-100 ppm total of major cations (Na, K, Mg>Ca)

Conclusion

To sum up, the reviewed basic strategic approach for method development by ICP-MS offers a comprehensive framework for researchers and analysts. By integrating fundamental principles and practical methodologies, this approach enables the systematic development of robust analytical methods tailored to specific applications. Emphasizing factors such as sample preparation, instrument optimization, calibration strategies, and quality control measures, it empowers analysts to achieve accurate and precise results while maximizing efficiency and minimizing variability. As ICP-MS continues to play a pivotal role in various fields, from environmental monitoring to pharmaceutical analysis, the adoption of this strategic approach promises to enhance method development processes, ultimately advancing scientific understanding and technological innovation.

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