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Why AAS Still Matters in the ICP-MS Era: Fit-for-Purpose Elemental Analysis for Pharmaceutical Quality Control

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Abstract
With the implementation of ICH Q3D and USP <232>/<233>, the pharmaceutical industry has moved away from the historical and nonspecific “heavy metals” test and toward a more meaningful, element-specific, risk-based approach. This change has resulted in the increased use of ICP-OES and ICP-MS for the determination of elemental impurities in drug products, APIs, excipients, and other pharmaceutical materials.

However, in making this transition, it is important not to assume that every elemental analysis question must now be answered by ICP-MS. Atomic absorption spectroscopy, including flame AAS and transversely heated graphite furnace AAS, remains useful in many pharmaceutical quality control applications. ICP-OES remains a very practical and capable technique for many multi-element applications, especially where the required limits are compatible with the sensitivity of the technique. ICP-MS, while extremely powerful, is not without its own limitations, particularly in relation to contamination control, matrix effects, interferences, and method validation.

The proper approach is not to select the newest or most sensitive instrument by default. Rather, the analytical method should be selected and validated based upon its intended use, the elements of concern, the matrix being analyzed, the required reporting limits, and the regulatory or compendial purpose of the test.

Keywords: atomic absorption spectroscopy; graphite furnace AAS; ICP-OES; ICP-MS; elemental impurities; ICH Q3D; USP <232>; USP <233>; pharmaceutical quality control; method validation

Introduction

In an effort to improve and modernize the control of elemental impurities in pharmaceuticals, the industry has moved from the older “heavy metals” approach to a more specific and scientifically sound framework. ICH Q3D(R2) establishes permitted daily exposures for elemental impurities and provides a risk-based process for assessing and controlling these impurities in drug products. The guideline considers the potential sources of elemental impurities, including intentionally added catalysts, raw materials, manufacturing equipment, utilities, and container closure systems.

USP <233>, Elemental Impurities—Procedures, describes analytical procedures for the evaluation of elemental impurities. Procedure 1 is based on ICP-AES/ICP-OES, and Procedure 2 is based on ICP-MS. These procedures have provided the pharmaceutical industry with a modern instrumental framework for elemental impurity analysis. However, they should not be interpreted to mean that other techniques, such as AAS or graphite furnace AAS, have no remaining value.

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At the outset, it is important to make a distinction between an elemental impurity risk assessment and a specific compendial or product-related assay. These are not always the same analytical problem. A multi-element elemental impurity screen under ICH Q3D may require one type of analytical approach. A monograph assay for zinc, magnesium, calcium, iron, sodium, potassium, or nickel may require another. In many cases, the older and more targeted technique may still be fully suitable for the intended purpose.

This issue was discussed by the author in the 2015 Contract Pharma Magazine article, "Elemental Impurities: Where we were then, where we are now, and where are we going?" In that article, the transition from historical heavy metals testing to the USP <232>/<233> and ICH Q3D framework was presented not simply as an instrumental change, but as a regulatory, validation, and GMP compliance issue.

Where We Are Now: Elemental Impurity Testing in Practice

The ICH Q3D approach is based upon risk. It does not require that every element be tested in every material under every circumstance. Rather, it requires that a scientifically justified risk assessment be performed and that elemental impurities likely to be present be controlled. The process is based upon knowledge of the product, its components, the manufacturing process, the equipment, catalysts, excipients, route of administration, and maximum daily dose.

This point is central to practical implementation. In practice, elemental impurity compliance is not simply a matter of buying an ICP-MS and running samples. The real work is in understanding the product, developing a suitable sample preparation procedure, demonstrating recovery, controlling contamination, evaluating interferences, and validating the method for the intended use.

This is also where many difficulties arise. Pharmaceutical products and materials are not all alike. Tablets, capsules, creams, suspensions, gels, powders, mineral-based excipients, botanical materials, colorants, inorganic salts, polymers, and packaging materials can each present different sample preparation and analytical challenges. A method that works well for one matrix may not work well for another.

Consequently, the analytical technique should be selected only after the analytical problem has been defined.

Flame AAS

Flame atomic absorption spectroscopy is one of the most mature instrumental techniques used for elemental analysis. It is relatively simple, well understood, and cost-effective. For many single-element assays, especially where the element is present at ppm or higher levels, flame AAS can be a very suitable technique.

Examples include assays or limit tests for elements such as zinc, magnesium, calcium, sodium, potassium, iron, copper, and nickel, depending upon the matrix and specification. In these applications, the use of ICP-MS may provide greater sensitivity, but greater sensitivity does not necessarily improve the quality decision. If the specification is at a level easily measured by flame AAS, and the method has been shown to be accurate, precise, linear, and suitable for the matrix, then flame AAS remains appropriate.

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This is especially true for compendial methods and legacy product specifications. Many of these methods were developed and validated using AAS. They may be included in product registrations, quality agreements, or internal control strategies. Replacing them with ICP-OES or ICP-MS may be possible, but it is not simply an instrumental substitution. It may require method validation, comparability work, change control, and in some cases regulatory or customer approval.

Transversely Heated Graphite Furnace AAS

Graphite furnace AAS, including transversely heated graphite furnace AAS, occupies an important position between flame AAS and plasma-based techniques. It provides significantly better sensitivity than flame AAS for selected elements, while remaining a targeted, element-specific technique.

In graphite furnace AAS, a small volume of sample is introduced into a graphite tube and subjected to a controlled temperature program. This includes drying, pyrolysis, atomization, and cleanout steps. Transversely heated graphite furnace designs improve temperature uniformity across the graphite tube and support more nearly isothermal atomization conditions. Published work on transversely heated graphite furnace AAS describes its use for rapid analysis and improved furnace performance.

This is not a trivial distinction. In graphite furnace AAS, the furnace program, matrix modifier, pyrolysis temperature, atomization temperature, background correction, injection volume, tube condition, and sample matrix can all affect the result. For example, EPA Method 7010 recommends the use of a stabilized temperature platform to maximize an isothermal environment within the furnace cell and to help reduce interferences.

For pharmaceutical work, THGA/GFAAS remains useful when only one or a few elements require low-level determination. It may be appropriate for lead, cadmium, arsenic, chromium, nickel, selenium, cobalt, thallium, or other elements, depending upon the required limit and sample matrix. It is also useful where sample amount is limited, where ICP-MS is not available, or where a validated furnace AAS method already exists.

However, graphite furnace AAS should not be viewed as a replacement for ICP-MS in broad elemental impurity screening. It is slower, more element-specific, and more dependent upon matrix-specific optimization. Its value is in targeted, low-level determinations where the analyte list is narrow and the method can be properly validated.

ICP-OES

ICP-OES, also referred to historically as ICP-AES, is a multi-element technique that uses an argon plasma to excite atoms and ions. The emitted light is measured at element-specific wavelengths. In pharmaceutical laboratories, ICP-OES is often a practical and highly useful technique.

ICP-OES has several advantages. It provides multi-element capability, good linear dynamic range, relatively good matrix tolerance, and high sample throughput. It is particularly useful for oral dosage forms, excipients, raw materials, inorganic salts, catalysts, mineral-containing materials, and samples where the elements of interest are present at moderate levels.

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One should not assume that ICP-OES is unsuitable simply because ICP-MS has lower detection limits. In many cases, ICP-OES can readily meet the required limits. The question is not whether ICP-MS can go lower. The question is whether ICP-OES can meet the required reporting limits with acceptable accuracy, precision, specificity, and robustness.

This was demonstrated by Menoutis, et.al. in their 2018 paper in the Journal of Pharmaceutical and Biomedical Analysis. The study evaluated axial-viewed ICP-AES with ultrasonic nebulization for selected elemental impurities in oral drug products. The authors reported that the use of axial ICP-AES with ultrasonic nebulization provided an alternative to ICP-MS for elemental impurity analysis requiring low detection limits, with element-specific limits of quantitation significantly lower than the PDEs for oral drugs.

This is an important practical point. ICP-OES should not be dismissed as a lesser technique. When properly configured, optimized, and validated, it can be a very appropriate method for many pharmaceutical elemental impurity applications.

ICP-MS

ICP-MS is the most sensitive of the commonly used elemental analysis techniques discussed here. It provides low detection limits, broad multi-element capability, isotope information, and the ability to measure trace and ultra-trace elemental impurities. It is often the preferred technique for ICH Q3D elemental impurity work, especially where low permitted daily exposures, low specification limits, high daily dose, or parenteral/inhalation routes of administration require very low reporting limits.

ICP-MS is especially useful for elements such as arsenic, cadmium, lead, mercury, cobalt, vanadium, nickel, and platinum group elements. It is also useful when an initial broad screen is needed to support a risk assessment.

However, ICP-MS is not without limitations. It is highly sensitive not only to the analytes of interest, but also to contamination. Reagents, labware, digestion vessels, laboratory environment, sample handling, and instrument memory effects can all contribute to background or bias. Matrix suppression, internal standard drift, polyatomic interferences, isobaric interferences, and collision/reaction cell conditions must be understood and controlled.

Thus, while ICP-MS is extremely powerful, it still requires method development and validation. It should not be treated as an automatic solution to every elemental impurity problem.

Why AAS Is Still Cited in Compendia

One of the questions often asked is why AAS remains cited in compendia when ICP-OES and ICP-MS are now widely available. The answer is that compendial methods are not replaced simply because newer instrumentation exists.

Many AAS methods were developed for specific materials and specific analytical purposes. They were validated, transferred, and used over long periods of time. In many cases, they remain suitable. If a monograph requires the determination of a single element at a concentration readily measurable by AAS, there may be no scientific need to replace that method with ICP-MS.

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Also, compendial procedures must be broadly usable. They must be capable of being performed by laboratories with different instruments, different resources, and different levels of capability. AAS remains widely available, relatively economical, and well understood. For specific assays and targeted limit tests, it can still provide reliable and defensible data.

However, this does not mean AAS is appropriate for every elemental impurity application. It is not. AAS is not the best choice for broad, multi-element, low-level screening. For that purpose, ICP-MS, and in some cases ICP-OES, will generally be more appropriate.

Sample Preparation: The Key to Method Performance

In most instances, sample preparation is the key to method performance. This is true regardless of whether the final measurement is made by AAS, THGA/GFAAS, ICP-OES, or ICP-MS.

Pharmaceutical samples can be difficult. Some dissolve readily. Others require acid digestion, microwave digestion, extraction, dilution, or matrix-specific preparation. Some materials do not fully digest under routine conditions. Some elements may be lost, converted to volatile species, precipitated, adsorbed, or affected by the acid system used.

This is one reason why the “referee procedure” concept can be misunderstood. A general procedure may provide useful guidance, but it may not be directly suitable for every API, excipient, or finished dosage form. If the sample preparation must be modified to address matrix-specific issues, then additional validation may be required.

The Menoutis JPBA study is relevant here as well, because the work employed closed-vessel microwave-assisted digestion in connection with ICP-AES analysis. The paper noted that osmium recovery was affected by formation of OsO_4 during microwave-assisted digestion, illustrating that sample preparation chemistry can affect specific elements even when the instrumental technique is otherwise suitable. For this reason, method suitability cannot be assumed; it must be demonstrated.

Method Validation and Suitability for Intended Use

From a GMP perspective, the central issue is not the name of the instrument. The central issue is whether the method has been shown to be suitable for its intended use.

For elemental impurity testing, this typically means that the method must demonstrate appropriate specificity, accuracy, precision, linearity, range, detection capability, quantitation capability, robustness, and system suitability or quality control performance, as applicable. The sample preparation procedure must also be shown to recover the elements of interest from the matrix being analyzed.

This is where method verification and method validation must be carefully distinguished. In some cases, a compendial procedure may be verified for use with a specific sample. In other cases, especially where the procedure is modified or the matrix presents difficulties, a fuller validation may be necessary.

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It is this writer's opinion that, in actual practice, many elemental impurity methods require more development and validation than originally expected. This is especially true for complex dosage forms, insoluble excipients, mineral-based materials, botanical materials, products containing pigments or colorants, and materials requiring aggressive digestion or extraction.

Practical Selection of the Technique

A practical approach begins with a clear definition of the analytical question. A good starting point is to define the analytical question. Is the purpose to support an ICH Q3D risk assessment? Is the purpose to comply with USP <232>/<233>? Is the purpose to perform a monograph assay? Is the purpose to test a raw material, an excipient, an API, a finished dosage form, a cleaning residue, or a packaging component? Is the element list broad or narrow? What reporting limits are required? What is the daily dose? What is the route of administration? What is known about the manufacturing process?

Once these questions are answered, the technique can be selected more rationally. Flame AAS is appropriate where the element list is short, the concentration is moderate, and the method is established or compendial.

THGA/GFAAS is appropriate where one or a few elements must be measured at low levels and a targeted furnace method can be properly optimized and validated.

ICP-OES is appropriate where multi-element capability is needed, the required limits are achievable, and matrix robustness is important.

ICP-MS is appropriate where low reporting limits, broad multi-element screening, or ultra-trace analysis is required.

In many laboratories, more than one of these techniques may be needed. They are not mutually exclusive. They are complementary.

Implications for Pharmaceutical Laboratories and Outsourcing

Many pharmaceutical companies do not maintain all of these capabilities internally. Some may have ICP-MS, but not graphite furnace AAS. Others may have AAS and ICP-OES, but not ICP-MS. Some may not have microwave digestion capability. As a result, outsourcing becomes an important part of elemental impurity compliance.

However, when outsourcing this work, it is important to consider more than whether the contract laboratory has the instrument. The laboratory should have experience with pharmaceutical matrices, sample preparation, method validation, contamination control, and GMP documentation. It should also understand when a method requires verification and when it requires validation.

In addition, contract laboratory capacity is not infinite. Method development, digestion work, validation, and routine GMP analysis all require time and qualified personnel. Waiting until a filing, inspection, or product release issue arises can create unnecessary difficulty.

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Closing Thoughts

Elemental impurity testing has clearly moved into a more scientifically sound and risk-based era. ICH Q3D and USP <232>/<233> have provided a much better framework than the historical heavy metals test. ICP-OES and ICP-MS are central to that framework, and ICP-MS in particular is indispensable for many low-level elemental impurity applications.

However, AAS has not become obsolete. Flame AAS remains suitable for many targeted assays. Transversely heated graphite furnace AAS remains useful for selected low-level determinations. ICP-OES remains a practical and powerful multi-element technique. ICP-MS remains the technique of choice for many trace and ultra-trace applications.

The best approach is not to force every sample onto one instrument. Rather, the best approach is to understand the product, the matrix, the elements of concern, the regulatory requirement, and the required method performance. From there, the appropriate technique can be selected and validated.

In the final analysis, the method must be suitable for its intended use. That remains the central requirement.

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