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Study of the use of axial viewed inductively coupled plasma atomic emission spectrometry with ultrasonic nebulization for the determination of select elemental impurities in oral drug products

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ABSTRACT

In efforts to control the potential presence of heavy metals in pharmaceuticals, the United States Pharmacopeia (USP) and International Conference on Harmonization (ICH) have put forth new requirements and guidelines for their control. The new requirements and guidelines establish specific daily exposures (PDE) for 24 heavy metals/elemental impurities (EI) based upon their toxicological properties. USP General Chapter ⟨233⟩ provides a general reference procedure for preparing pharmaceutical samples for analysis employing microwave assisted digestion (MWAD). It also provides two Compendial Procedures, Procedure 1 employing ICP-AES, and Procedure 2 employing ICP-MS. Given the extremely low detection limits afforded by ICP-MS, much work has been done in developing and evaluating analytical methods to support the analysis of elemental impurities in finished pharmaceutical products, active pharmaceutical ingredients, and excipients by this analytical technique. In this study, we have evaluated the use of axial ICP-AES. This employs ultrasonic nebulization (UN) for the determination of Class 1 and 2 EI, instead of traditional pneumatic nebulization. The study also employed closed vessel MWAD to prepare samples for analysis. Limits of quantitation were element specific and significantly lower than the PDEs for oral drugs. Spike recoveries for the elements studied ranged between 89.3% and 109.25%, except for Os, which was subject to OsO4 formation during MWAD. The use of axial ICP-AES UN provides an alternative to ICP-MS in the analysis of EI requiring low detection limits.

1. Introduction

Heavy metals pose chronic toxicological risks and their effects can be very difficult to detect. Growing concern over controlling potential heavy metals exposure has resulted in establishment of element specific daily exposure (PDEs) limits for finished drug products by both the United States Pharmacopeia (USP), International Conference on Harmonization (ICH), and other pharmacopial and regulatory bodies. These PDEs are based on current toxicological assessments of the elements rather than the capability of the testing methodology. There are 24 elemental impurities of potential concern identified by both USP⟨232⟩ and ICH Q3D. However, based upon the route of administration, oral, parenteral, inhalation, etc., not all of these 24 elemental impurities need to be monitored. Table 1 lists their PDEs by route of administration and classification, according to risk based upon toxicity and likelihood of occurrence. USP⟨232⟩ and ICH Q3D also provide guidance as to which of these 24 elemental impurities must be tested for. For example, an oral drug product need only be tested for Class 1 and Class 2A elemental impurities which total 7, assuming that through a paper risk assessment, no other elemental impurities are identified as contributory from the manufacturing process. If the use of a catalyst, such as silver, palladium or platinum is used in the manufacturing process, including raw materials such as excipients, then the additional 10 Class 2 B elemental impurities must also be tested for. Thus, if no further sources are identified, for an oral drug where catalysts are used in the manufacturing process a total of 17 specific elemental impurities out of the 24 must be tested for.

The compendial methods that have historically been used to determine heavy metals have relied on the precipitation of metal sulfides from an aqueous solution, and visual comparison to a lead standard similarly treated. In 2008, the USP proposed replacing the historical compendial method for heavy metals ⟨231⟩ with two new General Chapters. These two chapters, ⟨232⟩ Elemental Impurities- Limits and ⟨233⟩Elemental Impurities-Procedures, respectively, establish safety based limits on elemental impurities

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Table 1
Established Permitted Daily Exposures (PDEs) for Elemental Impurities.

Element	Class	Oral PDE ug/day	Parenteral PDE ug/day
Cd	1	5	2
Pb	1	5	5
As	1	15	15
Hg	1	30	3
Co	2A	50	5
V	2A	100	10
Ni	2A	200	20
Tl	2B	8	8
Au	2B	100	100
Pd	2B	100	10
Ir	2B	100	10
Os	2B	100	10
Rh	2B	100	10
Ru	2B	100	10
Se	2B	150	80
Ag	2B	150	10
Pt	2B	100	10
Li	3	550	250
Sb	3	1200	90
Ba	3	1400	700
Mo	3	3000	1500
Cu	3	3000	300
Sn	3	6000	600
Cr	3	11000	1100

and modern methods for their analysis. Following several years of revisions with input from industry and regulatory stakeholders, these two chapters were issued in final form, being subsequently harmonized with ICH Q3D, and industry compliance beginning in January 1, 2018.

Prior to the development of USP⟨233⟩, Wang [1] and Lewen [2] had proposed and demonstrated that ICP-MS could be used as a rapid screening technique for heavy metals in pharmaceutical compounds and materials. This, along with Lewen's involvement on the USP Expert Committee developing ⟨232⟩ and ⟨233⟩ led to the inclusion of both ICP-AES and ICP-MS as the referee methods. More recently, the use of ICP-MS for the determination of the original 15 elemental impurities covered by ⟨232⟩, but also the additional 9 included in ICH Q3D guidelines, and subsequently added by USP to ⟨232⟩ and ⟨233⟩, was demonstrated by Li [3] for the analysis of these 24 elemental impurities in pharmaceutical excipients.

In November 2011, Dr. Heather Joyce, of USP, presented a talk titled "Elemental Impurities – Development of Modern Analytical Procedures", at the Eastern Analytical Symposium held in Somerset, New Jersey. In her presentation, she spoke about the approach taken by USP in the preliminary development of the analytical procedures in ⟨233⟩. She mentioned that the initial approach taken was based upon the United States Environmental Protection Agency (USEP) methods for the analysis of trace metals in the environment, such as EPA's superfund analytical methods.

The use of atomic spectrometry as an analytical technique has found widespread use for the analysis of trace metals in the environment since the mid 1970s. The USEPA has developed numerous methods for using flame atomic absorption spectrophotometry (AAS), graphite furnace atomic absorption spectrophotometry (GFAAS), ICP-AES, and ICP-MS. In 1974, the first commercial ICP-AES instrument was introduced, which employed a radially viewed plasma. By 1994, there were 9000 systems installed, and just 10 years later, over 17,000 had been installed in laboratories worldwide. The vast majority of these systems were employed in monitoring trace metals in the environment, while at the same time, only 4000 ICP-MS systems had been installed [4].

In efforts to improve detection limits take while taking advantage of the rapid, multi-element capabilities of ICP-AES for environmental and plant analysis, development of improved introduction systems were undertaken. This led to the substitution of ultrasonic nebulization (UN) with aerosol desolvation for the conventional pneumatic nebulization used in ICP-AES [5–7]. Using UN with aerosol desolvation, Berman and co-workers were able to analyze five trace metals in seawater using ICP-AES with a detection limit of 1ug/L [8]. Subsequent work by Fassel and Bear [9] resulted in further improvements on UN with aerosol desolvation, ranging in improved detection limit factors from 5 to 50. Using a commercial UN with aerosol desolvation, Galli and Oddo were able to obtain detection limits that rivaled GFAAS and ICP-MS for 17 trace metals in solutions having 0.1%-1% dissolved solids, as NaCl [10]. Uchida, et al. were able to demonstrate the applicability of ICP-AES UN for the analysis of biologic tissue, plant, nutritional supplements and food stuff samples [11], while Kukaya, et al. demonstrated that ICP-AES UN could be effectively employed in the analysis of trace metal impurities in high purity copper [12]. The application of ICP-AES UN to the analysis of heavy metals in herbal medicines [13], phytopharmaceuticals, and pharmaceutical derivatives [14] was demonstrated by Gomez, et al. An improvement to radial viewed plasma ICP-AES, were the plasma is viewed side-on, is axial viewed plasma ICP-AES. In this mode, the spectrometer looks down through the plasma rather than across it as in the radial view. Hoeing, et al. [15] and Masson, et al. [16], employed axial viewed plasma ICP-AES with ultrasonic nebulization obtaining detection limits for many elements, in environmental and plant samples, respectively, equaling those capable by ICP-MS.

The aim of the present research was to study the analysis of elemental impurities, Class 1, 2A and 2B, in an oral drug requiring low detection limits employing axial ICP-AES UN.

2. Experimental

2.1. Reagents and materials

Concentrated nitric acid (70%, v/v, trace metal grade) and concentrated hydrochloric acid (36%, v/v, trace metal grade) were purchased from Fisher Scientific, and used throughout this work to prepare standards and samples. Hydrogen Peroxide (30%, v/v) Trace Element Analysis Grade, was purchased from Sigma-Aldrich (St. Louis, MO, USA). Ultrapure water with a resistivity of 18.2MΩ used in the experiments was prepared by passing water through deionizer polishing filters, and then through a Milli-Q Type 1 Ultrapure water system (EMD Millipore, Billerica, MA, USA). Standard solutions for elemental analysis were prepared by diluting commercially available, NIST traceable, single element 1000 mg L^{-1} stock solutions (Inorganic Ventures). Spike solutions for recovery assessment were also prepared from these stock solutions. Yttrium was used as an internal standard, and was prepared from 1000 mg L^{-1} stock solution (Inorganic Ventures).

Test samples employed for this study consisted of two oral drugs, generic aspirin, 81 mg, and Lisinopril, 20 mg.

2.2. Sample preparation

The oral drugs were prepared by as per USP⟨233⟩. Briefly, 0.2 g of the oral drug was weighed into a microwave digestion vessel. Pre-digestion was initiated by adding 3.0 mL of nitric acid with the careful addition of 1.0 mL of hydrogen peroxide to each vessel, and waiting 10 min for the reaction to subside. After 10 min an additional 4.0 mL of nitric acid was added, along with 2.0 mL of hydrochloric acid. Each vessel was then assembled and carefully sealed tight. Samples were then subjected to closed vessel microwave digestion allowing sample decomposition under high temperature and pressure. A modified microwave digestion program was used employing a two-step microwave program consisting of a 5 min ramp to 210 °C, with a hold for 5 min; then a 3 min