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Applications of inductively coupled plasma-atomic emission spectrometry (ICP-OES) in impurity profiling of Pharmaceuticals

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Abstract

Pharmaceutical impurities are unwanted chemicals that remain or are generated during the formulation or upon aging of Pharmaceuticals. Some common sources which can cause contamination of pharmaceuticals with elemental impurities during their development and manufacture are catalyst residues from the synthesis of drug substances or released elements from storage and manufacturing equipment. These unidentified potentially toxic impurities are hazardous to health. In order to increase the safety of drug therapy, it is important that concentration of impurities in pharmaceuticals is controlled and kept at a low level. However determination of trace quantities of impurity is a challenge. ICP-OES is emerging as an important tool in the determination of trace elemental impurities in various sample matrices. ICP-OES provides higher sensitivity, lower detection limits, less chemical interferences and is less time consuming as compared to other spectrometric techniques. Continuous wavelength coverage by ICP provides dynamic range and reduced interferences, giving accurate results. Robust plasma in ICP-OES ensures reliable results even with most complex matrices. ICP-OES have several merits which include a higher atomization temperature and ability to perform simultaneous determination. Simultaneous multi-elemental analysis increases throughput and productivity, as compared to other techniques like atomic absorption spectrometry (AAS) using both flame and graphite furnace atomic absorption spectrometry(GFAAS). Present study focuses on the various ICP-OES techniques developed to measure trace metal content of active pharmaceutical ingredients (API), intermediates and finished formulations and its future adaptability in pharmaceutical industry for routine use to perform simultaneous determination of trace elements in Pharmaceuticals.

Key words: Heavy metals; elemental analysis; quantisation; impurity profiling; atomic spectroscopy

Introduction

Pharmaceutical impurities in active pharmaceutical ingredients (API) or additives are unwanted chemicals that remains in the formulation or are generated during the formulation or are produced on aging of both API and formulated APIs.[16,22] One of the common contaminants of major concern are elemental impurities in Pharmaceuticals. Some common sources which can cause contamination of pharmaceuticals with elemental impurities during their development and manufacture are catalyst residues from the synthesis of drug substances or release of elements from storage and manufacturing equipment.[6, 22]

Traces of inorganic impurities can reduce drug stability and shelf life of some pharmaceutical products. Metal ions can catalyse the degradation of active pharmaceutical ingredients (API) and cause unequalified degradants to form, or pose a toxicity threat on their own.[8] These unidentified potentially toxic impurities are hazardous to health and in order to increase the safety of drug therapy, it is important that concentration of impurities in pharmaceuticals is controlled and kept at a low level. Therefore different pharmacopoeias slowly incorporating the limits of allowable level of elemental impurities present in API and formulations.[1,19] The U.S. Food and Drug Administration(FDA) and the British Pharmacopoeia (BP) strictly advice that contamination problems be fully investigated in a timely fashion according to the specifications.

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Inductively coupled plasma-atomic emission spectrometry (ICP-OES)

Utility in determination of elemental impurities

The control of elemental impurities has always been a critical issue to pharmaceutical industry.The Pharmacopoeias prescribe the test for heavy metals to keep a check on level of elemental contaminants particularly heavy metals to ensure safety. These analytical procedure have certain deficiencies including inability to differentiate between the levels of individual contaminants. Secondly, recoveries are alarmingly low.[11] Therefore, recently United State Pharmacopeia has replaced the chapter of chapter <231>*Heavy metals*limit test replaced by two new chapters <232>*Elemental impurities – Limit*[4] and <233>*Elemental impurities – Procedures*[5] . The analytical procedures in these two new chapters are based on inductively coupled plasma techniques being much more specific and sensitive. ICP-OES has proved to be an important tool in the determination of elemental impurities in various sample matrices and is now used in pharmaceutical industry to measure trace metal content of active pharmaceutical ingredients (API) or intermediates against specification limits specified in various pharmacopoeias.[21] ICP-OES provides higher sensitivity, lower detection limits, less chemical interferences and is less time consuming as compared to other spectrometric techniques. Continuous wavelength coverage by ICP provides dynamic range and reduced interferences, giving accurate results. Robust plasma in ICP-OES ensures reliable and reproducible results even with most complex matrices. Simultaneous multi elemental analysis increases throughput and productivity.

Advantages of ICP OES as compares to other instrumental techniques

ICP-OES have several merits as compared to other available instrumental technique i.e atomic absorption spectrometry (AAS). These include a higher atomization temperature, a more inert environment, and ability to perform simultaneous determination for up to 70 elements. This makes ICP less susceptible to matrix interferences. In cases where sample volume is not limited, ICP-OES provides detection limits even less than AAS. Due to impressive characterstics of ICP as an analytical atomic emission source, many of other emission sources such as direct current plasma (DCP), microwave induced plasma(MIP), flame, laser induced plasma(LIP), electrical discharge etc have been restricted to narrower areas of applications. The main analytical advantages of ICP over other excitation sources are because of its capability for efficient and reproducible vaporization, atomization, excitation and ionization for a wide range of elements in various sample matrices. The high temperature (6000-7000 K) of ICP allows it to excite even refractory elements. ICP is less noisy and is an electrode less source, so there is no contamination from electrode material.[8]

Working principle and Instrumentation

ICP/OES technique is based upon the spontaneous emission of photons from atoms and ions that have been exited in a RF discharge. These photons have characteristic energies that are determined by the quantised energy level structure for the atoms and ions. Thus the wavelength of photons can be used to identify the elements from which they originated. The total number of photons is directly proportional to the concentration of the originating element in the sample.

In this technique, liquid samples are injected into the central channel of radiofrequency (RF) induced argon plasma using one of the variety of nebulizers or any other sample introduction techniques in the form of aerosol. Liquid or gas samples may be injected directly into instrument, where as solid sample require extraction or acid digestion. At its core ICP sustains very high temperature (8000-10000K) so the aerosol is quickly dried and vaporized. Analyte elements are liberated as free atoms in the gaseous state. Further collisional excitation within the plasma imparts additional energy to the atoms to convert them to ions and promoting them to excited states. Both excited atoms and ions may then relax to the ground state by emitting photons. The photons by ICP is collected with a lens or a concave mirror. This focussing optic forms an image of ICP on the entrance aperture of a wavelength selection device such as monochromator. The particular selected wavelength is then converted into an electrical signal by a photodetector. The signal is amplified and processed by detector electronics then displayed and stored by a personal computer.

Single element detection can be performed by using simple monochromator/ photomultiplier tube (PMT) combinations but for performing simultaneous multielement determination (upto 70 elements) the combination of a polychromator and an array detector is used.

ICP source also called as ICP "torch": It comprises of three concentric fused silica quartz tubes – the outer, intermediate and the inner gas tube. The argon stream that carries the sample, in the form of aerosol, passes through the inner tube. The excitation is provided by water cooled, two or three turned copper coil, called load coil which surrounds the top section of the torch, and is connected to a RF generator. A radiofrequency

current (frequency ~ 27 MHz or 40MHz) flows through the load coil.

The outer argon flow (10 -15Lmin^{-1}) sustains the high temperature plasma, and positions the plasma relative to the outer walls and the induction coil, preventing the walls from melting and facilitating the observation of emission signals. It is this gas stream that is excited by the radiofrequency power (700-800W). The plasma under these conditions has a characteristic torroidal shape in which the sample is introduced into relatively cool central hole of the torus at a slower rate (1ml/min). The sample aerosol carried by the inner argon flow (0.5-1.5 Lmin^{-1}) enters the central channel of the plasma and helps to sustain the shape.

The plasma is initiated by a spark from a Tesla coil which produces a "seed" electrons and ions in the argon gas inside the load coil region. These electrons and ions are than accelerated by the magnetic field, and collide with other argon atoms, causing further ionization in a chain reaction manner. This process continues until a very intense high temperature plasma is formed. The ICP is sustained within the torch as long as sufficient RF energy is applied.[11] This addition of energy to the plasma via RF induced collision is known as inductive coupling.[12]

There are two ways of viewing the light emitted from an ICP. In the classical ICP-OES configuration, the light across the plasma is viewed radially, resulting in the highest upper linear ranges. By viewing the light emitted by the sample looking down the center of the torch or axially, the continuum background from the ICP itself is reduced and the sample path is maximized.

Sample Preparation

Elemental analysis by inductively coupled plasma – atomic emission spectrometry requires sample to be injected in either liquid or gas phase. Whereas solid samples require extraction or digestion prior to injection.[8] There are various digestion process used for elemental analysis of samples like tube dry ashing, wet ashing, microwave assisted digestion(MAD), high pressure asher (HPA) digestion. For some mineral samples fusion method had also been used.[25]

However, sample preparation in closed vessel like MAD is preferred as compared to open vessel digestion due to many advantages like shortening of digestion time and liberation of small amount of corrosive acid vapours.[12,14,20] Another approach for sample preparation utilizes the direct dissolution in a solvent. By applying this approach sample handling time can be minimised which further reduces the chances of cross contamination along with the lessening the sample preparation time.

Detection and detection limits

The detection limits achievable for individual elements are important in determining the usefulness of an analytical technique for a given analytical problem. Without adequatedetection-limit capabilities, lengthy analyte concentration procedures may be required prior to analysis.Typical detection-limit ranges for the major atomic spectroscopy techniques are shown in Table 1. For a complete listing of detection limits by element for Flame AA, GFAA, ICP-OES (with radial and axial torch configurations) and ICP-MS.

Table 1: Detection limit ranges

S. No	Atomic Spectroscopy Technique	Detection Limit Ranges (ppb)
1	Flame AA	1-100
2	ICP-OES (Radial)	0.1-100
3	ICP-OES (Axial)	0.01-10
4	Hydride Generation AA	0.01-0.1
5	GFAA	0.01-10
6	ICP-MS	0.001-1

Application of ICP in heavy metal detection in drugs, pharmaceuticals and food supplements

Drug research, development and production is dependent on elemental analysis, starting with the testing of individual ingredients and continuing through production to final quality control. For the analysis of raw materials and components to finished product testing and quality control, industrial and chemical manufacturers require accurate analytical techniques to ensure the safety and performance of their products. Instrumentation for accurate measurements of metals in biological matrices is vital when assessing human exposures to natural and synthetic chemicals. Currently researchers are developing ICP OES techniques for elemental analysis in various pharmaceutical sample matrices as shown in table 2.

Table2: Application of ICP OES in the field of Pharmaceuticals

Elements Detected	Bulkdrug/ formulation/food supplement	Sample preparation Procedure	Medium	Reference
Cd,Cr, Pb	Polymers	High pressure asher digestion (HPA)	HNO_3	Cho & Myung2011
Ca,P	Eliphos tablets	------	-----	Venkata2011

B	Tamsulosin Hydrochloride	Dry ashing	Calcium Hydroxide saturated solution	Rajput *et al*2010
W	Bulk drug & intermediate	Dissolution	80:20(v/v) HNO_3	Wang *etal* 1999
Ru	Catalyst material	Microwave digestion	6:1 (v/v)HCl/HNO3	Suoranta *et al*2014
Al, Ca, C, Cu, Cr, Fe, k, Mg, Mn, Na, Ni, P, Zn	Laterite and surpentine minerals	Microwave assisted total acid digestion	HCl+HNO3 +HF	Pena *et al*2014
Cu, Mg, Zn	Escitalopram oxalate	Dissolution	0.5% HNO3	Veeramachaneni & Jayavarapu 2013
Mo, Se	Infant formula	Dry ashing Wet digestion Microwave	25ml conc HNO3 + 2ml H2O2 7:1 (v/v) HNO3/H2O2	Khan *et al* 2013
Na, K,Ca, Mg, Al, B, Ba, Co, Cr, Cu, Fe, Li, Mn, Mo, Ni, Pb, Sr, V	Pure hydroxides and salts	Direct determination	-------	Krejcova *et al* 2006
Cr, Cu, Fe,Mg, Mn,Zn,Al,Cd, Pb	Legumes	Wet digestion Dry ashing	(i)2:1(v/v)HNO3/H2SO4 (ii)4:1:1(v/v)HNO3/H2SO4/ H2O2	Momen et al 2006

Cho & Myung reported determination of Cd, Cr, Pb in polymers by ICP-OES using a high pressure asher technique for digestion at pressure and temperatures up to 13MPa and 130^0C. Validation parameters such as linearity, matrix effect, limit of detection LOD), limit of quantitation (LOQ), accuracy and precision were assayed.[3]

Venkata et al reported a validated Inductively coupled plasma-Optical emission spectrometry (ICP-OES) method to estimate free calcium and phosphorus in *in vitro* phosphorus binding study of Eliphos tablets.[26]

Rajput et al reported a method for quantitative determination of Boron content in Tamsulosin Hydrochloride using Inductively coupled plasma-Optical emission spectrometry. They proposed that the method can be easily adopted for routine quantitative analysis of Boron.[17]

Wang et al developed a quick and sensitive method for the determination of tungsten in bulk drug substances and intermediates by ICP-AES and ICP-MS. The method was validated as per ICH guidelines.[28]

Suoranta et al compared various digestion methods for the determination of ruthenium in catalyst material using ICP-OES. They compared a fusion method, an acid digestion method and two microwave assisted digestion methods for their suitability in the determination of ruthenium in catalyst material[24]

Pena et al reported multielemental Inductively coupled plasma-Optical emission spectrometry analysis of nickeliferous minerals. The study describe the methodology for the simultaneous quantitative determination of Al, Ca, Co, Cu, Cr, Fe, K, Mg, Mn, Na, Ni, P and Zn in nickeliferous minerals.[15]

Veeramachaneni and Jayavarapu developed and validated a new ICP-OES analytical technique to quantify the contents of copper, magnesium and zinc in Escitalopram oxalate. The method is found to be

selective and is capable of detecting copper, magnesium and zinc in presence of other elements.[27]

Khan et al developed and validated a method for simultaneous determination of chromium, molybdenum and selenium in infant formulas by ICP-OES and ICP-MS.[10]

Momen et al investigated four digestion procedures for multi-element determination of toxic and nutrient elements in legumes by inductively coupled plasma-optical emission spectrometry[13]

ICP-OES also finds wide spread applicability in other fields. In the environment we live in, understanding heavy-metal contamination is critical. The accurate measurement of concentrations of these metals is imperative to maintain clean air, water and soil for a safer world. Accurate analysis of food for nutritional content, contamination or authenticity – the exact geographic source of the product –is critical for regulatory and quality assurance. From petroleum refining to a broad spectrum of applications using lubricants and oils, many industries require the determination of metals – particularly analytes that can lead todegradation and contamination – to ensure conformity as well as monitor and control processes.With myriad applications from date stamping to precious metals testing, ICP-OES offers a fast, accurate solution for broad geological surveys as well as an invaluable means oftesting potential mining areas before incurring the high costs associated with digging. Trace metals are essential for plant growth. ICP-OES also facilitates precise soil analysis to ensure that metals are not at levels that could unduly affect the food source (livestock and/or crops).Operating under constant scrutiny, the nuclear field is required to monitor and measure the levels of a variety of elements to an exacting degree. Atomic spectroscopy preferably ICP-OES is commonly used to determine trace elements in everything from process water to low-level waste. As the world continues to move toward eco-friendly technologies and energy sources, there's an ever-increasing need for accurate elemental analysis. Applications include testing biofuels for batch consistency and quality control, as well as trace elemental analysis on solar panels to ensure optimum performance.

Conclusion

Various regulatory authorities like ICH, USFDA, Canadian Drug and Health Agencies are emphasizing on the identification of impurities in active pharmaceutical ingredients as presence of impurities even in small amounts may influence the efficacy and safety of the pharmaceutical products. The present study focuses on various advantages and applications associated with ICP-OES for identification as well as quantification of impurities present in the pharmaceuticals. ICP-OES is proved to be an advanced technique for impurity profiling of pharmaceuticals with lower detection limit and high sample throughput.

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