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A REVIEW ON THE RECENT APPROACHES FOR THE ANALYSIS OF ELEMENTAL IMPURITIES BY ICP-BASED TECHNIQUES

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ABSTRACT

The main objective of this paper is to study and analyse the ICP-based techniques currently used for control of various pharmaceutical products quality by analysing elemental impurities. In this study, the key benefits, detection limits, interference, and sensitivity of various ICP-based techniques are established by comparing them with other techniques. The development of a novel approach to obtain accurate, precise, efficient and reliable results for the analysis of elemental impurities in finished drug products is one of the major challenges of modern pharmaceutical quality control research and development.

Based on the recent incident in Eluru town, West Godavari District (Andhra Pradesh) on Dec 5th 2020, At least 550 individuals have fallen ill with common symptoms of anxiety, nausea and vomiting. AIIMS findings suggest that the potential cause for people becoming ill is uncontrolled lead (Pb) and nickel (Ni) content in drinking water or milk. Therefore analysis of elemental impurities and control of their PDE levels are extremely significant.

We can monitor and modify the possible source of elemental impurities in pharmaceuticals by using ICP-based techniques, contributing to simple drug products that are impurity-free. Growing interest in the elemental impurities analysis is attributable to the fulfilment of the regulatory requirements of the current prescribed limit standards, as in the case of pharmacopoeias.

Keywords: Elemental Impurities, Inductively coupled plasma and Regulatory requirements.

INTRODUCTION

ICP is a high-temperature ionisation source that dissolves atoms from vaporisation, excitation, and ionisation and is specifically used to excite atoms to higher energy levels or to produce ions. In pharmaceutical products, elemental impurities have been regulated for decades[1].The primary application of ICP is specific, multi-elemental analysis with sensitivities down to ppb and ppm levels. The leaching of elemental entities also produces elemental impurities in drug products[2].

To prevent severe dangerous effects, the analysis of elemental impurities is very important. For example, at least 550 people have recently fallen sick in Eluru town, west Godavari district (Andhra Pradesh) on Dec 5th 2020. The Indian Institute of Medical Sciences (AIIMS) team carried out blood tests for at least 550 individuals and a preliminary report (AIIMS), Delhi, discovered presence of elemental impurities lead (Pb) and nickel (Ni) in at least 10 blood samples obtained from patients of different localities. The results indicate that the lead and nickel content of drinking water or milk is a potential cause for people falling ill. Seizures, tremors, anxiety, vomiting, nausea, anxiety, frothing, loss of consciousness and headache are common symptoms seen in infected individuals. Children, in particular, reported a sudden onset of vomiting after complaining about burning eyes.

On the basis of the degree of PDE (allowed dose exposure) and the probability of occurrence, the elements are classified into three categories. Spectro chemical elemental analysis meets the latest requirements

announced by ICH for pharmaceutical products and raw materials used for manufacturing[3] .

The appropriate alternatives for rapid and accurate multi-elemental analysis are inductively coupled plasma (ICP)-based techniques and can be applied for speciation analysis. It is also possible to consider ICP-based methods as a recent trend in determining elemental impurities[4].

ICP-based techniques for elemental impurity analysis are highly preferred and selective because of their peculiar characteristics, consistent efficiency, highly reliable, precise, and sensible results and their way of handling different analytical tasks. Various elemental impurities in drug products are clearly mentioned in Table 1.

PDE concept has been clearly established by the Q3C Residual Solvents Guideline of the International Harmonization Council (ICH). The PDE levels are primarily focused on the existing toxicological evaluation of components[4].

2. Methodology

2.1 ICP-based techniques

At higher temperatures (from 6000K to 10000K), ICP-based techniques are characterised, allowing most elements to be optimised and ionised. The gases used for plasma production include Ar, He, and N_2. The introduction of samples is very flexible: solids, liquids and gases in plasma can be ionised. When combined with chromatographic techniques such as GC, LC and capillary electrophoresis; these methods are sensitive regardless of chemical form.

Sample preparation methods

As specified in pharmacopoeia, sample preparation methods require several steps and the use of different reagents, low throughput and a high risk of contamination. The three main techniques are combustion, wet digestion, and direct dissolution into aqueous or organic solvents.The most effective method used for ICP-based techniques is matrix digestion, aimed primarily at degrading organic compounds and minimising spectral interferences[5].

Extraction methods are considered as alternatives, since most of the elemental impurities are not included in the chemical composition of active pharmaceutical ingredients. Cloud point extraction (CPE) and ultrasound extraction techniques are used for liquid samples and a microwave-assisted approach to solids samples.

Solid samples can be analysed using LA (laser ablation) and ETV systems, with the majority of ICP methods focusing on solution analysis[5]. Various sample preparation methods and steps are clearly viewed in Figure 1.

Wet digestion

The most common method for matrix digestion is a solution composed ofanalytes and matrix components that should be incompletely or fully oxidised by treating the sample materials with oxidant reagents (conventionally heated or by microwave radiation). It is primarily used, with higher digestion efficiency and rapid heating, in organic matrix sample preparation.

Mixtures of HNO_3 with HCl, HF, $HClO_4$, $H2SO_4$, and H_3PO_4 are usually favoured. HNO_3 and H_2O_2 are used for the analysis of elementary impurities in some APIs, respectively.Wet digestion is often carried out in closed polytetraflouroethylene vessels and the sample mass varies from 100 to 300 mg. The temperature used should be above 300^0c for a high-pressure Asher system.

Combustion

In ICP-based research, these techniques basically allow the matrix to be destroyed and the carbon effects to be reduced. But some of the problems were identified due to the risks of loss of analyte and contamination. And they can prevent digest incompatibility with ICP-based techniques[5].

The primary benefit of this approach is the suitability of dilute solutions to maintain the elements evolved from the sample during combustion efficiently. . But for more ICP-based research, closed vessels are suitable. Analysis of simple impurities based on the ICP-MS system uses MIC (microwave-induced combustion). Because MIC has the ability to apply reflex phase immediately after sample combustion without analyst intervention or Instrument modification[5].

MIC in closed vessels is mainly proposed for the “hard to digest” samples[6]. An Advanced technique focused MIC is developed with a combination of commercial focused microwave oven and lab-made quartz sample holder, modified glass vessel[7].

Speciation analysis

First discussed by Forstner in 1993. It is the process of separation, evaluation and quantification of an element's various chemical forms.Speciation techniques that are most sensitive, selective, and precise are considered useful for ICP-MS and ICP-AES. This technique is mainly used to determine API impurities in order to evaluate species produced during synthesis, products of degradation, and in vivo metabolites.

Main downside of the study of speciation is that it is a complex task and requires multiple analytical steps, such as extraction, derivitization, preconcentration, clean-up, separation, and final detection.

Challenges in the determination of elemental impurities

The key challenge to establish a universal approach for the assessment of elemental impurities are a broad range of physical and chemical properties of API, human and environmental, a toxicological effect, due to different particularities. These essential impurities can catalyse and shorten the shelf-life of Active Pharmaceutical Ingredients(API'S) decomposition and can cause various un-desirable consequences that finally leads to poisoning of human body[8].

Solid sampling is the best choice for almost all elemental impurities using ICP-OES and ICP-MS techniques to prevent sample processing and to conduct direct analysis with good results using LA or ETV devices.

Advantages of ICP techniques

Rapid simultaneous multi-elemental analysis, lower detection limits, broad linear dynamic range, relatively small inter-element matrix effects, and high accuracy, applicable to analysis of solids, liquids and gases and elemental trace analysis. High sample throughput, professional outcomes and availability of validated processes are the main advantages of ICP-based techniques. Various advantages are clearly shown in figure 2.

Drawbacks

Spectral interference, matrix effects from solvent and concomitant species, inefficient sample initiation, drift, and insufficient precision for certain applications. Non-spectral interference can cause signal enhancement or depression. Spectral interference is observed when other species are detected either at the same wavelength or same m/z ratio. These are major drawbacks of ICP-based techniques. Drawbacks are clearly viewed in figure 3.

Basic steps in ICP-based analysis

First, by plasma, a sample may be dissociated into atoms, ions, and then it excites them to a higher degree of energy level. At a distinctive wavelength, they emit light, and then they analyse the light emitted. Lastly, the method can understand the concentration of metals inside the sample using standard solutions in figure 4.

Functional parts of ICP

There are several components of an ICP-6000 spectrometer, such as sample introduction parts (nebulizer, spray chamber, pump, centre tube, torch), gas control (argon), radio frequency power generator, optical system, polychromator, thermoelectric cooling, CID detector, and interlocks. Functional parts are clearly shown in figure 5.

2.2 Types ofAnalytical Techniques for analysis of elemental impurities

Various types of analytical techniques are clearly shown in figure 6.

Inductively coupled plasma-Atomic emission spectroscopy (ICP-AES)

Key theory involved in principle of this technique is that, by using the high-temperature ionisation source (ICP) electrons present in an atom absorbs the energy and excited to higher energy levels. While returning to their normal states, they emit characteristic photons of energy. By isolating these emitted photon wavelengths, we can determine the types and concentrations of elements present.As industry standard requirements for the ICP-AES method for analyzing inorganic elemental impurities, the latest US FDA and EMA regulations entered into force in 2018[9].

The sample to be analysed in the ICP-AES is drawn up by a peristaltic pump and converted into a fine aerosol by a nebulizer. Typical problems seen in ICP-AES are, however, spectral interferences, matrix effects, instrumental drifts and sampling difficulties, sample preparation. Inorganic lead speciation(Pb2-) and other tri-alkyl lead species can be examined using HPLC with ICP-AES detection[10].

Sample dissolution for solid samples is done by

Salt fusion

Salts such as sodium peroxide and lithium metaborate are mixed into the sample. That offers a high concentration of a sample atmosphere that dampens any differences in the inter-sample matrix. But it is not possible to quantify the readily volatilized elements.

Acid digestion

In an acid matrix, the sample is dissolved (nitric, hydrochloric acid) and is usually heated to accelerate dissolution. In general, the safest approach to metals, as opposed to direct dissolution, is to avoid the possible introduction of pollutants. But it is time-consuming.

Microwave digestion

Basically, acid digestion is carried out in vessels with controlled temperature and pressure. Typically, samples are dried, ashed, if necessary, and ground before dissolution procedures to 74µ.

The key strengths of the ICP-AES technique are rapid simultaneous elemental analysis, lower detection limits down to parts per trillion for some elements, appropriate for routine multi-sample analysis, and also an effective screening method for ICP-MS samples.

This technique can measure up to 60 elements simultaneously with wide linear dynamic range, which is considered to be an outstanding feature of ICP-AES. For tablets, this technique is used in the quantitative determination of various elements, such as Cu, Cr, Hg, Mn, Ni, Pb, Pd, and Zn.

However, matrix-related problems, acceptable standards required for each run, and providing only basic data, but not clear structural details, are the main drawbacks of this technique.

Schematic diagram of working of ICP-AES is shown in figure 7.

Microwave plasma- Atomic Emission spectroscopy (MP-AES)

In order to analyse the elementary composition of the sample by measuring its electromagnetic spectrum or mass spectrum, some analytical techniques, such as flame absorption atomic spectroscopy (FAAS), microwave plasma-atomic emission spectroscopy (MP-AES, ICP-AES and ICP-OES, works on the theory of atomic spectroscopy.

MP-AES is the atomic emission technique. The nitrogen-fuelled microwave plasma can reach a temperature of up to 5000k and acts as a source of atomic emissions. And these higher temperatures provide efficient atomic emissions, excellent detection limits, and linear dynamic range for most of the elements.

If an atom of a particular element is excited, the key concept involved in this process is that it emits light as it returns to the ground state in a characteristic wavelength pattern (emission spectrum). The key advantages of MP-AES over FAAS techniques are reducing ongoing operating costs, increasing safety, enhancing analytical efficiency, and simplifying operations.

MP-AES produces reactions that are reliable and precise. This approach has moderate to elevated efficiency and low operating costs. Overall, the MP-AES approach is the best choice for elemental impurity analysis in terms of sensitivity, speed of analysis, multi-elemental analysis, low operating costs and improving the safety of the laboratory environment by the use of non-flammable nitrogen. So that MP-AES can be run unattended in remote locations and produces very powerful plasma capable of handling a wide range of sample types using magnetic fields instead of electric fields, MP-AES operates efficiently on air, thus dramatically reducing ownership costs and eliminating the need for continued supply of flammable or expensive gases.

Difficult matrices are easily handled by the robust, magnetically excited microwave plasma (MP-AES source). The primary advantages of this method are quicker measurements, delivering timely data with valuable benefits, preventing spills, and improperly manufactured products. Instead of a laboratory, .MP-AES can be placed at a sampling point and is suitable for remote operation.This technique is also ideal for analysing components such as Cd, Cu, Pb, Ti and Zn in different textile fibres such as cotton and polypropylene[11].

MP-AES systems include special software applet applications that can automatically load a pre-set process. So, we can start the study immediately with minimal preparation and no need for any method formation or alignment.

Thanks to the improved efficiency of the higher temperature source of nitrogen plasma, which provides high tolerance to the organic solvent load, the requirements for acetylene and nitrous oxide can be eliminated along with storage and handling problems. MP-AES is the first liquid-liquid extraction process to determine the pre-concentration of elemental impurities in water[12].

The greater linear range of the MP-AES instrument eliminates the need for sample over-range dilution, thus simplifying sample analysis. And enhanced linearity means less calibration standards are required for an effective calibration curve. MP-AES will greatly simplify the sample preparation process, saving money and time.

MP-AES systems have a multimode sample introduction system (MSIS) that makes it possible to use either vapour generation or nebulization mode or both modes to implement samples at the same time. This technique demonstrates promising performance as a quantitative analytical technique and has application in various fields such as food, health, agriculture and pharmaceutics[13].

The MP-AES method should focus on its drawbacks like poor robustness and should develop novel spectrometer for the simultaneous measurement of wavelengths[13].

Laser ablation-Inductively Coupled Plasma- Mass spectrometry (LA-ICP-MS)

In order to extract material from a solid sample surface, Laser Ablation (LA) uses a directed laser beam. This is a special technique for rapid screening of elemental impurities with a daily dosage of less than 2.0g in solid pharmaceutical products. LA-ICP-MS is a powerful analytical tool, especially for the analysis of solid samples.

This approach is mainly used to evaluate elements such as Pb, As, Co, Ni, Pd, Rh, Pt, Cd in strict compliance with the USP and ICH Q3D Guidelines and has undergone successful validation in terms of linearity, accuracy, range, limit of detection (LOD), intermediate precision and range[14].

The most preferred technique for elemental impurity analysis is validated LA-ICP-MS for various types of solid pharmaceutical products such as API'S, placebo, excipients, and finished drug products.

On the other hand, the LA-ICP-MS technique has some disadvantages, such as the difficulty of choosing an acceptable set of international standards needed to reduce signal variance between samples and sample homogeneity. Agilent 7700x ICP-MS fitted with an ASX-520 auto sampler was carried out to test the total elemental impurities. This method is also appropriate for the multi-elemental in-situ quantitative analysis of sulphide minerals[15] .

For the analysis of elemental impurities in pharmaceutical products, sensitive LA-ICP-MS methods fulfil the pharmacopeial requirements. But for therapeutic purposes, certain components such as Bi, Cu, Fe and Mn are purposely incorporated into drug products[16].

For the analysis of elemental impurities in pharmaceutical products, sensitive LA-ICP-MS methods follow the pharmacopoeia requirements. The key benefits of this technique are elemental fractionation, easy qualitative analysis, good calibration standards, minimal sample preparation, and a simplified matrix that avoids spectral interferences. The main ability of LA-ICP-MS is to evaluate conductive, non-conductive, opaque and transparent materials[17].

Certain problems occur in calibration and representativeness, making quantitative analysis more difficult. However, only minimal data treatment is needed and maximum information is provided regarding the average concentrations of the sample analytes[18].

LA-ICP-MS is a rapid advanced analytical technique for analysing different trace elements and contributes to a major role in advancing the study of geochemistry[19].

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

The fundamental concept involved in working of ICP-OES is that a source of high temperature ionisation excites atoms to higher energy levels (ICP). They emit light that is observed by a photometer at a wavelength characteristic of a specific element as these atoms decay down to lower energy levels. The ICP-OES system is primarily beneficial for oral dosage types.There is a need for a large sample volume (no dilution) and high throughput. This technique utilises vertical plasma for axial and radial emissions. Therefore, it provides excellent sensitivity and high matrix capability.

The Laser Induced Breakdown Spectroscopy (LIBS) or ICP-OES technique is mainly known for its intrinsic conceptual simplicity and versatility[20]. Introducing samples can also be an important source of random and systemic errors in ICP-OES sample measurement[21].

ICP-OES has the capability of automated method development comprising of plasma parameter optimization tool. It establishes effective self-monitoring methods and needs less frequent calibration. Certain matrix effects are observed in the ICP-OES. Methods of sample preparation were developed by a mixture of 65 percent HNO_3 and 37 percent HCl (3:1 v/v) by microwave-assisted acid digestion.

For six repeated blank samples, the LOD was calculated to 3 times of standard deviation, while the LOQ was calculated to 10 times of standard deviation for the measured concentration[22].

Internal standards, the match matrix, the internal addition process, the acceptance and removal of calibration errors, the control of experimental parameters, the design of modern elemental analysis systems, the production of smart instruments and the use of chemical metric calibration are some of the techniques used to reduce sample-induced errors.

Trace metal analysis requires a new micro-wave sample introduction method to be developed. Method precision was tested by performing long-term stability tests. For fast routine analysis, dilute-and-shoot procedures are appropriate[23].

In order to quantify the presence of elemental impurities in a diverse collection of samples, the ICP-OES approach offers low-cost multi-elemental analysis. It shows advanced performance with high productivity and ensuring compliance with global regulations leading to consistently precise outcomes. This means that analysts with any degree of

experience and without any user interface complications can work easily.
Easily Analyses the demanding samples with the help of self-optimizing robust plasma tool by the swing frequency Rf generator and provides effective analytical performance and stability. Minimal preparation is adequate for the required team and rapid instrument start-up increases performance.
Accessories are simplified and can be easily connected to the sample introduction technique, which significantly expands the power and efficiency of the instrument.
Higher sample throughput, less maintenance and auto dilution saves the time and cost of analysis. The simple workflow minimises the steps taken to carry out a mission, leaving more time for analysts to focus on other activities. The ICP-OES system is used to determine the presence of minute quantity impurities and gallium content in plutonium metals with enhanced accuracy, precision and detection limits[24].
The ICP-OES instrument is also appropriate for the dilute-and-shoot technique to determine different elemental impurities in pharmaceutical liquid samples.To correct the matrix results, however, customised calibration methods are needed, enabling the dilute-and-shoot technique to be applied to 10-hold diluted samples and making the elemental impurity analysis of liquid drugs feasible by ICP-OES. Schematic diagram of working of ICP-OES is shown in figure 8.

Inductively coupled plasma-mass spectrometry (ICP-MS)
(Combination of high-temperature ICP source with Mass - spectrometer)
The first method of choice for multi-elemental analysis with an excellent detection limit (LOD), precision, selectivity and broad linear range, high sample throughput with the possibility of analyzing solid, slurry and liquid samples, is an ICP-MS technique with adequate sample preparation.Simultaneous multi-elemental speciation analysis of arsenic, antimony and tellurium is performed by an anion exchange HPLC-ICP-MS technique[25].
It mainly consists of a hard source of ionisation to break down any molecule into constituent atoms which are then ionised in plasma (argon plasma at atmospheric pressure).
The unique advantage of using this technique is that the element's ionisation is not dependent on the chemical composition of the forming compound. Thus, ICP-MS is used for quantitative purposes since the same criterion does not need to be used for each analyte. With strong detection capabilities, it is a highly sensitive, accurate and selective device.
The method implementation and validation quality control of analytical procedures are defined in USP chapter<233>[26]. The lower LOD (detection limit) values in ng/liter are known for this process. And it has a broad linear calibration range, from 6 to 9 orders of magnitude, applicable for ultra-trace analysis. Used for routine analysis in the pharmaceutical industry's quality management department[27]. Various Instrumental conditions of ICP-MS are clearly listed in table 2.

The most commonly used ICP-MS instruments are
ICP-QMS (quadrapole analyser as a mass filter).
ICP-SFMS (double-focusing sector field mass spectrometer).
FI-ICP-QMS (flow injection -ICP-Quadrapole MS).
FI-ICP-TOFMS flow injection-ICP-time of flight MS).
HPLC-ICP-MS (for elemental speciation tasks)
The key principle involved in the process of ICP-MS is the 'conversion of element atoms in the specimen to positively charged ions' by a high-temperature ionisation source (ICP) and these ions are classified and separated by a mass spectrometer based on their mass-to-charge (M/Z) ratio and directed to the detector. Several elements are analysed at the sub-ppb, sub-ppt, and sub-ppb-ppm levels.
In addition, for the detection of organic and inorganic species, chromatographic methods such as HPLC can be coupled to ICP-MS. And many samples can be tested at a time and the sample quantity should be > 5 ml.
ICP-QMS with vapour phase dissolution (VPD) was used to dissolve high-purity arsenic by acid vapours prior to the characterization of trace elements[28].
ICP-MS is a highly precise and selective technique, but it requires highly qualified personnel and high acquisition costs, so not much is used compared to ICP-OES. The ICP-MS technique, however, overcomes the disadvantages of ICP-OES in assessing As and Pb at low concentrations with high precision because of its lower LOD values.ICP-MS for protein qualification and quantification is also an appealing alternative to electron spray MS and MALD[29].
This approach is applicable to all dosage forms (parenteral, inhalation and oral administration), unless the ICP-OES is identical. And only a small number of samples are required, but larger dilutions are required. ICP-MS methods are not only applicable for the study of elemental impurities, but also for

the different trace elemental analysis in pharmaceuticals[30].

For the rapid and simultaneous analysis of elements like Os, Rh, Ru, Cr, Ni, V, Cu, Ir, and Zn in drug products by prior dilution, dissolution or microwave-assisted closed vessel digestion in accordance with the mentioned regulations, a flow injection ICP-QMS/SFMS technique is used. For the speciation analysis of selected halides, ICP-MS is also suitable[31].

ICP-MS is also suitable to the elemental analysis of wine, but due to some non-spectral interferences and plasma instability, it is a challenging task[32].

The main advantages of flow injection-based techniques are

Reduction in sample intake by up to 50 microliters (advantageous for limited and expensive samples), increase in sample throughput by minimising time for analysis, decrease in time and effort for sample preparation, low consumption of high purity chemicals and a clear sample digestion method will be seen often.

For the rapid and precise analysis of elements like As, Hg, Ru, Cr, Pt, Mo, Ni and Mn in drug products by prior dilution, a novel technique based on flow injection analysis is mainly preferred[33].

Solid sampling feasible by LA-ICP-MS, detection limits down to parts per quadrillion for some materials, are the key benefit of this high-resolution ICP-MS technique. LA-ICP-MS is a feasible method for quantitative elemental data acquisition and spatially resolved portion mapping in biological tissues[34]. A Clear Comparison of parameters of ICP-MS and ICP-OES/AES are clearly listed in table 3.

Instrumental Neutron Activation Analysis (INAA)

For the qualitative and quantitative determination of elemental impurities, INAA is an isotope-specific analytical technique. The fundamental theory of neutron activation research is the conversion by neutron irradiation of stable atomic nuclei to radioactive nuclei and subsequent identification of gamma radiation emitted during the decay of radioactive nuclei. The INAA approach is especially suitable for the direct determination of rare earth elements like Th, Ta and U[35].

INAA is a primary technique that, without reference to a standard of the same quantity, calculates the value of an unknown element. INAA is one of NAA's most critical analytical approaches, because it is sensitive and non-destructive[36]. So, the element can be used for other analytical techniques. The application of purely instrumental procedures is commonly referred to as INAA.

The isotope neutron sources that are common are 252Cf and 242Am. INAA is a gamma-ray spectroscopic system consisting of a multi-channel analyzer, an analog-to-digital converter, a detector, a preamplifier, a spectroscopy amplifier, and an output device. In the trace analysis of rare earth elements , INAA is the method of choice based on the nuclear properties of the elements to be determined[37].

Elements that are systematically determined by the INAA technique are Fe, Co, Ni, Zn, Cd, As, Br, Th, Ce, Lu, and Ag.Small sample sizes of up to 1 to 200 mg are adequate and chemical preparation is not required.Therefore, the sensitivity of this method is dependent on the sample matrix. 75% of the traditional remedies used by Chinese individuals were subjected to INAA's trace element survey study[38]. A Schematic diagram of working of INAA technique is clearly shown in figure 9.

Atomic Absorption Spectrometry (AAS)

AAS is a selective research method capable of measuring element concentrations up to parts per billion (ppb) of a gram in a sample. This technique focuses primarily on the characteristic wavelengths of light directly absorbed by the atoms present in an element that correspond to the energies needed for electrons to be promoted from one energy level to a higher energy level.

Elements in an atomic state that need to be analysed should be. Atomization transforms the sample into free atoms, irrespective of its initial state. AAS is appropriate for the study of elements like Se, As, Cd, Te and Hg at the level of ng/L[39]. After microwave-induced digestion, flame absorption spectrometry (FAS) was especially preferred for the determination of Cu, Mn and Zn[40].

In the AAS technique, sample preparation is always easy and the chemical form of the element is usually not considered. The relationship between the amount of light absorbed and the analyte concentration present in known standards, can be used to measure unknown concentrations of elements by measuring the amount of light absorbed.Sample digestion, description of pyrolysis and atomization temperatures, LOD determination and validation parameters are used in the analysis of selected drugs[41].

An atomic absorption spectrometer is a simple method that operates on this fundamental principle applied to practical quantitative analysis. But the atomization stage may be affected by the other chemicals in the sample that are present. There are two types of

atomization-atomization of flames and graphite furnace.In carbon nanotubes, some of the metallic impurities such as Co, Mg, Al and Pb were determined by direct solid sampling of electro thermal AAS[42].
Portable X-RF sensors in soil samples have the capacity to predict exchangeable nutrients[43]. But the major drawback of AAS technique is being a single-element analysis method.

The interferences that are encountered in the AAS technique are
Ionization interference
Lower radiation absorption is created by the creation of ions rather than atoms. And this problem is supressed by adding ionisation suppressors.

Self-absorption
Atoms of the same form that absorbs radiationcan absorb more at the middle than at the edges, causing the spectral line and its intensity to change.

Absorption of source radiation
The wavelength used can be absorbed by elements other than of interest.

Background absorption of source radiation
The existence of incomplete atomization particles was responsible for that. And by increasing the temperature of the flame, this problem is solved. A Schematic diagram of working of AAS is clearly shown in figure 10.

X-ray fluorescence spectrometry (X-RF)
In recent times, when compared to other analytical techniques, X-RF analysis has become increasingly attractive, especially because of the ease of sample preparation. The basic theory involved in the process of X-RF Spectrometry is that the elements emit X-rays when a sample is irradiated by high energy excitation X-rays.
Since electrons undergo transitions from higher to lower atomic energy levels, as the energy emitted is proportional to the element's binding energy, characteristic X-rays are unique to each element. X-RF spectra mainly based on continuous wavelet transform filters, is a new technique for the determination of toxic elements in pharmaceutical products by using hand-held XRF spectrometers[44].
For solids, powders, and liquid types of samples, the X-RF technique is sufficient. It is a non-contact analysis and procedure that is non-destructive. So, after measurements, the samples can be reused. In different drug product APIs, both the Energy Dispersive X-RF Technique (ED-XRF) and the Wavelength Dispersive X-RF Technique (WD-XRF) was successfully applied to the determination of elements like Zn, Fe, and Ni.X-RF has applications over both ultra- trace element analysis and surface analysis[45].
Besides of their higher detection limits, X-RF techniques are not very effective for quantitative determination of elemental impurities in pharmaceutical products. High reflectivity on flat surfaces and lower penetration depth of the main radiation are the two characteristic characteristics of total X-RF[45].

Advantages of the X-RF technique
High speed of the operation and ease of convenience. Compared to other classic methods, X-RF has greater precision and accuracy. Spectra are fairly transparent and not subject to much intrusion. It is a strategy which is non-destructive.

Limitations of X-RF technique
For the detection of light elements (with a lower atomic number), this approach is not sufficient. The high cost of instruments. The concentration range ranges between 0.01 and 100%.

3. RESULTS AND DISCUSSION
After observing principles, parameters and working of various analytical techniques (ICP and NON-ICP) techniques, ICP -based techniques(ICP-MS, ICP-OES, LA-ICP-MS, MP-AES and ICP-AES) are most preferred for rapid, accurate , precise and multi-analysis of various elemental impurities like Pb, As, Zn, Ni, Cd and Th in pharmaceutical and natural products. The Principles of various techniques and advantages of ICP over Non-ICP techniques are discussed in the following tables.

4. CONCLUSION
It is a difficult job to determine elemental impurities. The development of analytical techniques for the rapid elemental analysis will be a useful research activity in the upcoming years.
The benefits of these ICP -based techniques over conventional pharmacopoeia-defined limit tests and Non-ICP techniques,helps in leading to the adoption of these methods by various manufacturers. And the need of analysing elemental impurities in pharmaceutical products and daily needs has become a necessary application in these recent years in order to avoid severe dangerous effects to human health. A small negligence can lead to severe health problems (based on recently

happened Eluru town incident, West Godavari district, Andhra Pradesh).
So, ICP-based techniques are more advantageous comparing to non-ICP methods for the effective and accurate analysis of various elemental impurities.

5. OUTLOOK

Their unique features make them ideal for routine analysis; And ICP-based techniques have gained widespread use. There are several options for sample preparation available, including water or organic solvent dissolution, wet digestion, and microwave heating extraction, resulting in sufficient LODs for all pharmaceutical-related components. And there is need to improve the applicability of ICP-based techniques for effective elemental impurities analysis in upcoming years.

6. Abbreviations

ICP- Inductively coupled plasma
AAS- Atomic Absorption Spectroscopy
X-RF- X-Ray fluorescence spectrometry
INAA – Instrumental neutron Activation Analysis
OES- Optical Emission Spectrometry
LA- Laser Ablation
MP- Microwave plasma
GC- Gas chromatography
LC - liquid chromatography
CPE- Cloud point extraction
CE - Capillary electrophoresis

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Availability of supporting data
Not applicable

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All my co-authors have equally contributed for this manuscript design of work, data collection, analysis and interpretation, drafting and critical revision of the article and final approval of the version to be published.

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Table 1: List of elemental impurities in drug products

S. NO	Elemental impurities	Oral daily dose PDE (µg/day)	Parental daily dose PDE (µg/day)	Inhalational daily dose PDE (µg/day)
1	Lead	5	5	5
2	Cadmium	5	2	2
3	Inorganic mercury	30	3	1
4	Inorganic arsenic	15	15	2
5	palladium	100	10	1
6	Platinum	100	10	1
7	Chromium	11000	1100	3
8	Nickel	200	20	5
9	Vanadium	100	10	1
10	copper	3000	300	30

Table 2: Instrumental conditions for ICP-MS

S.NO	Parameters	ICP-MS value
1	Injector	2 mm i.d quartz
2	RF power	1600W
3	Neb gas flow rate	0.34 ml/min
4	Make up gas flow	0.7 ml/min
5	Sample uptake rate	0.01-0.04 ml/min
6	Dwell time	50 µs
7	Settling time	0 s
8	Analysis time	60 s
9	Measured isotopes	Pt, Au

Table 3: Comparison between ICP-MS and ICP-OES/AES

S.NO	Parameters	ICP-MS	ICP-AES/OES
1	Linear dynamic range	Up to 10^8 permits levels of detection sub-ppt-ppm levels	Up to 10^6 permits levels of detection sub-ppm to 1000ppm
2	sensitivity	High	low
3	Vaporization interferences	Fully absent	Fully absent unlike AAS
4	Quantification principle	Ionized species by quadrapole mass separation with intensity using m/z system	Measuring the light intensity emitted at a specific wavelength to the element of interest
5	Advanced features	Axial field technology, auto lens, dual-stage detector	Sequential, simultaneous, matrix-induced suppression
6	Multi elemental determination	High productivity	Optimal productivity
7	Isotopic ratio determination	capable	Not capable
8	Speciation capability	feasible	Feasible
9	Cost of analytical technique	High because of rapid semi-quantitative analysis	Cheaper but with high detection limits
10	Consumption of Ar gas	higher	Lower
11	Non spectroscopic interferences	Suppression and enhancement	Salt formation on cones Matrix induced suppression
12	Robustness in terms of total dissolved salts in solution	Not effective which will influence the nebulizer system	Highly robust even in presence of 20% dissolved salts
13	Multiple analytical fields of determination	Pharmaceutical, natural, clinical, and tissue imaging	Purity and impurity determination
14	limitations	The destructive technique, spectroscopic interferences	The non-destructive technique, database software pre-program

Table 4: Principles of various techniques

S.NO	Technique	Principle
1	**ICP-OES**	The fundamental theory involved in the action of ICP-OES is that a high-temperature ionisation source excites atoms to higher energy levels (ICP). As these atoms decay down to lower energy levels, they emit light that is observed by a photometer at a wavelength characteristic of a specific element.
2	**ICP-MS**	ICP-MS is the best method for the determination of elemental impurities in pharmaceuticals. It consists primarily of a hard ionisation source to break down any molecule into constituent atoms that are then ionised in plasma (argon plasma at atmospheric pressure).
3	**ICP-AES**	ICP-AES principle is mainly based on energy absorbed and excited to higher energy levels by using an atom's high-temperature ionisation source (ICP) electrons. They emit characteristic photons of energy as they return to normal states. Types and concentrations of elements can be determined by observing isolated photon wavelengths.
4	**MP-AES**	Works on the theory of atomic spectroscopy to determine the elementary composition of the sample by analysing its electromagnetic spectrum or mass spectrum.
5	**LA-ICP-MS**	Laser Ablation (LA) uses a focused laser beam to remove material from a solid sample surface. This is a unique technique for rapid screening of elemental impurities in solid pharmaceutical products with a daily dose of less than 2.0g.
6	**X-RF**	The theory involved in the process of X-RF Spectrometry is that the elements emit X-rays when a sample is irradiated by high energy excitation X-rays. Since electrons undergo transitions from higher to lower atomic energy levels, as the energy emitted is proportional to the element's binding energy, characteristic X-rays are unique to each element
7	**AAS**	This technique focuses primarily on the characteristic wavelengths of light directly absorbed by an element's atoms, which correspond to the energies required from one energy level to a higher energy level to promote electrons**.**
8	**INAA**	The basic principle involved in neutron activation research is the conversion of stable atomic nuclei to radioactive nuclei by neutron irradiation and subsequent detection of gamma radiation released during the decay of radioactive nuclei.

Table 5: Advantages of ICP-based techniques over Non-ICP based techniques

S.NO	Features	ICP methods (ICP-MS, ICP-OES, LA-ICP-MS, ICP-AES)	Non ICP methods (INAA,X-RF,AAS)
1	Detection limits	Excellent for most of the elements at ppb levels	Very good for some elements at ppm levels
2	Sample throughput	Less than one minute	5-6 minutes
3	Spectral and matrix interferences	Very few	few
4	Sample volume	Very small to medium	large
5	cost	Very high	Moderate to high

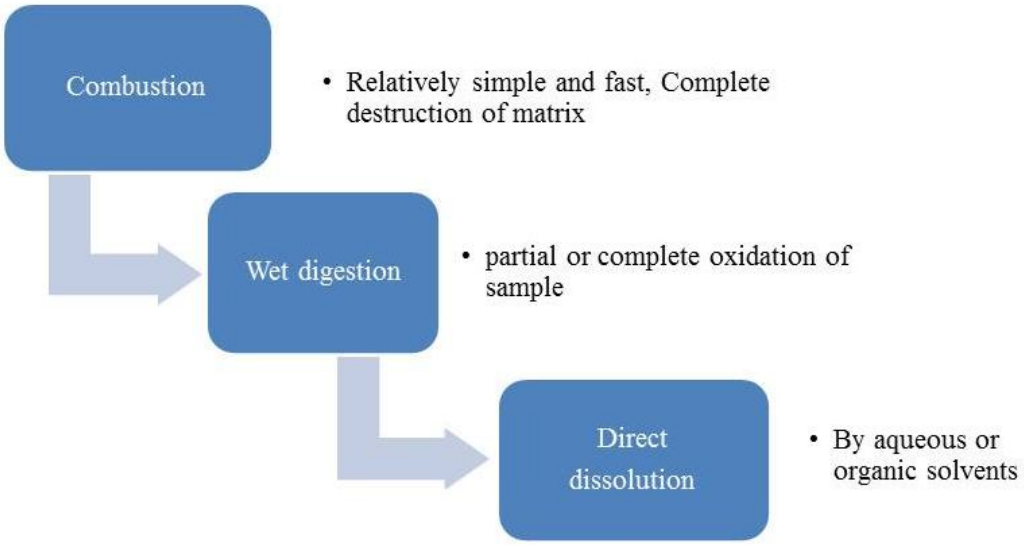

Fig. 1: Sample preparation methods

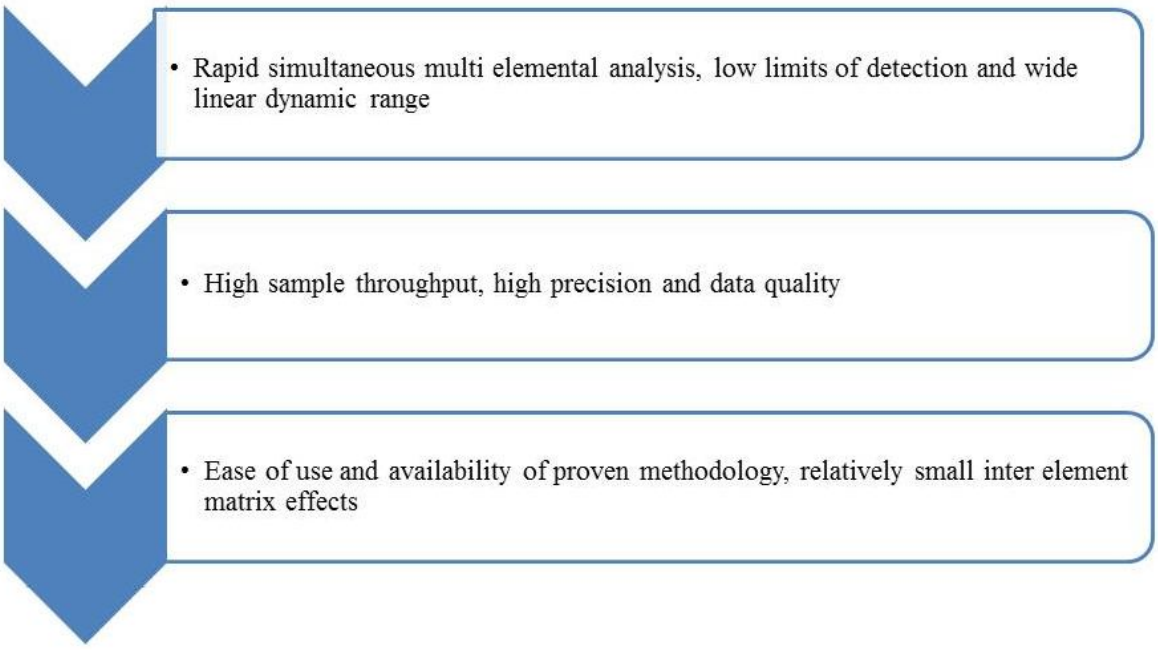

Fig. 2: Advantages of ICP-based techniques

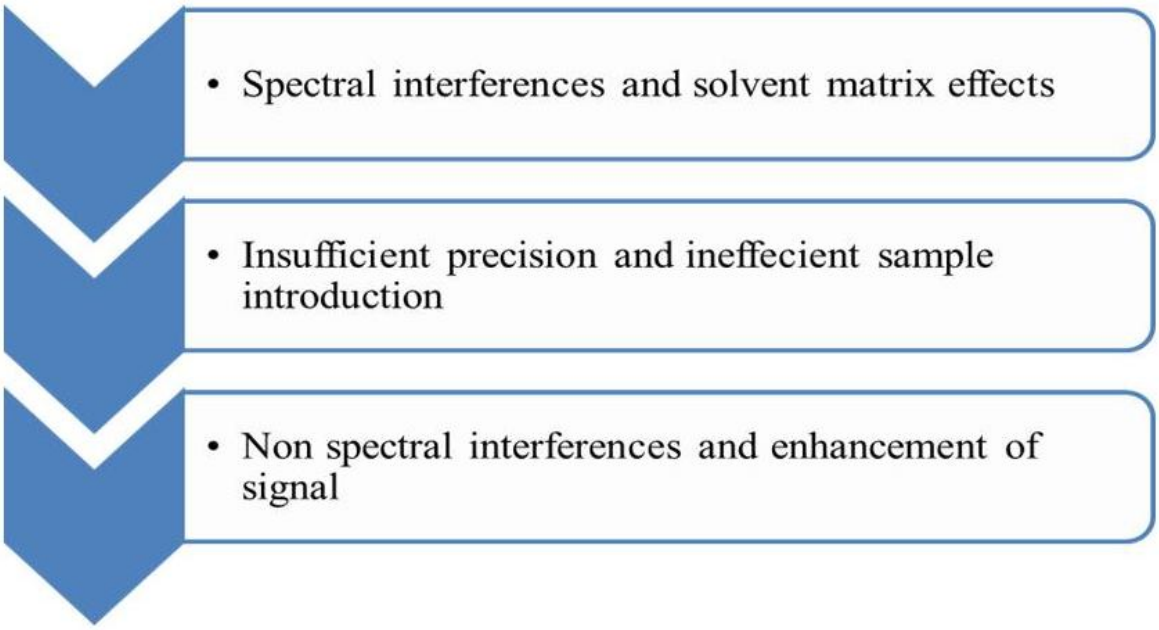

Fig. 3: Drawbacks of ICP - based techniques

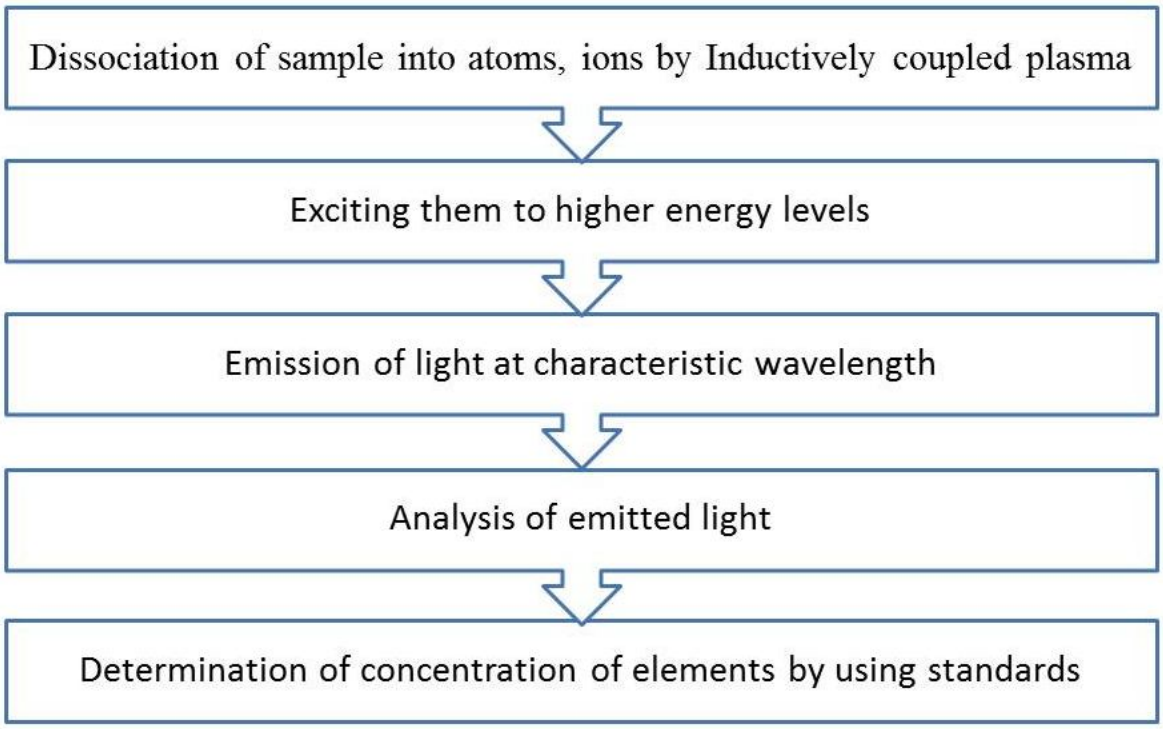

Fig. 4: Basic steps in ICP-based analysis

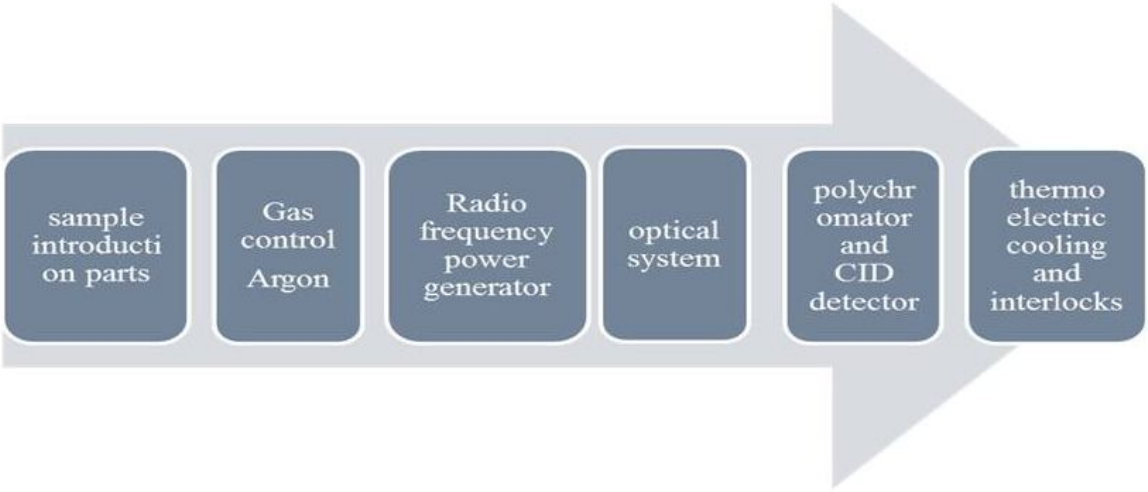

Fig. 5: Functional Parts of ICP

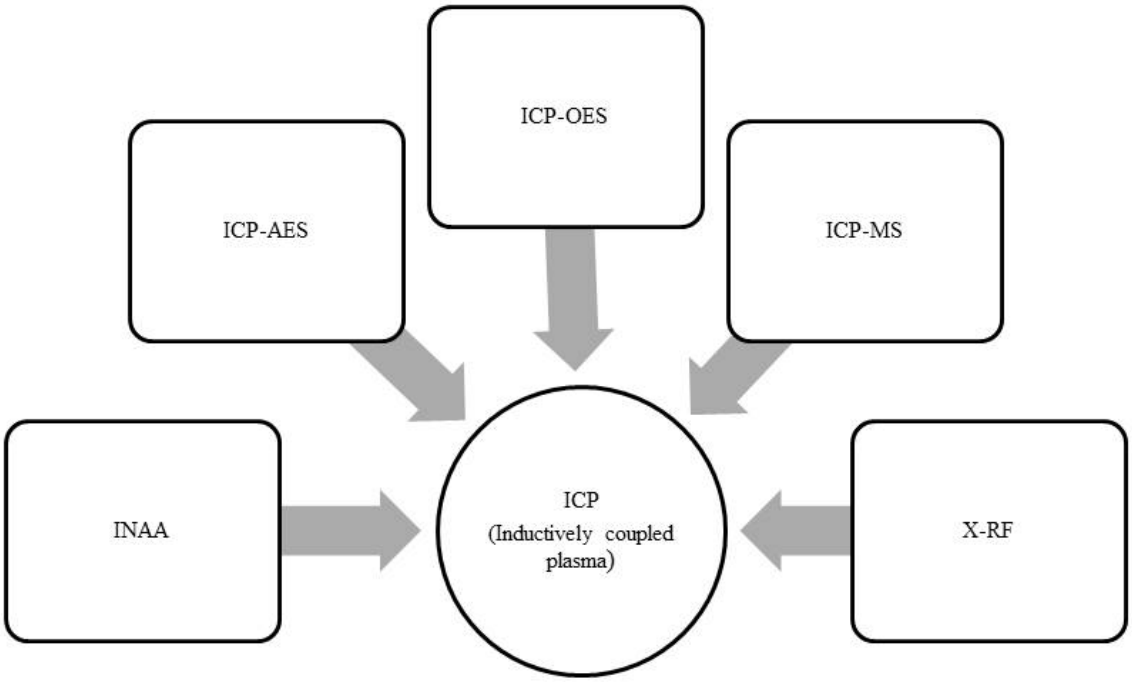

Fig. 6: classification of ICP- based techniques

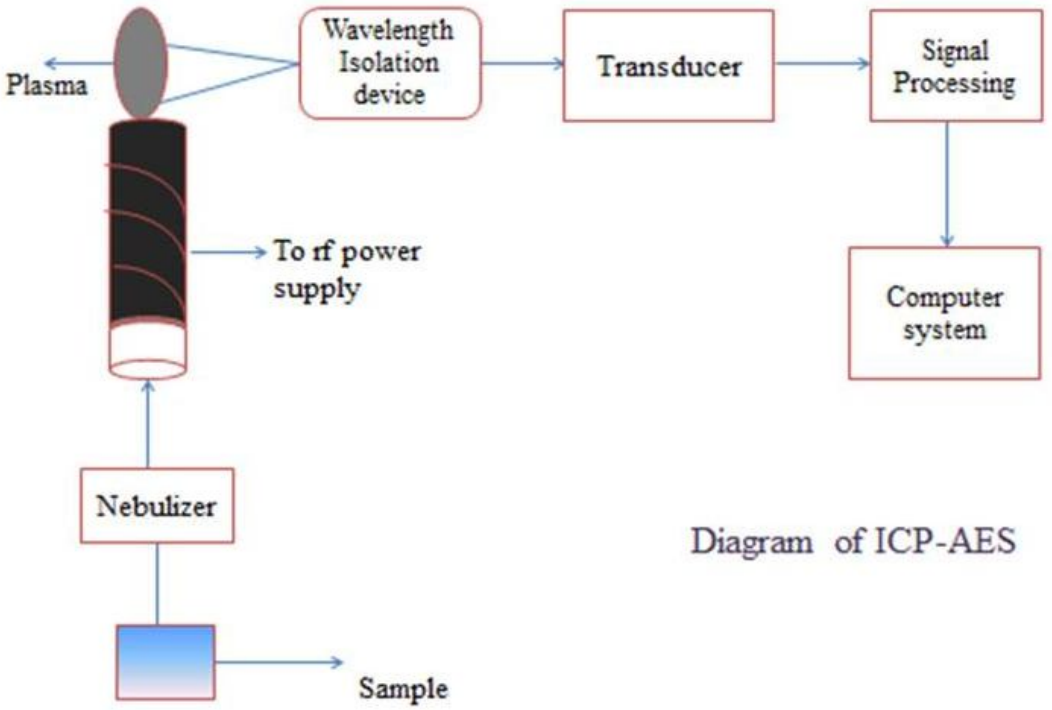

Fig. 7: Schematic diagram of ICP-AES

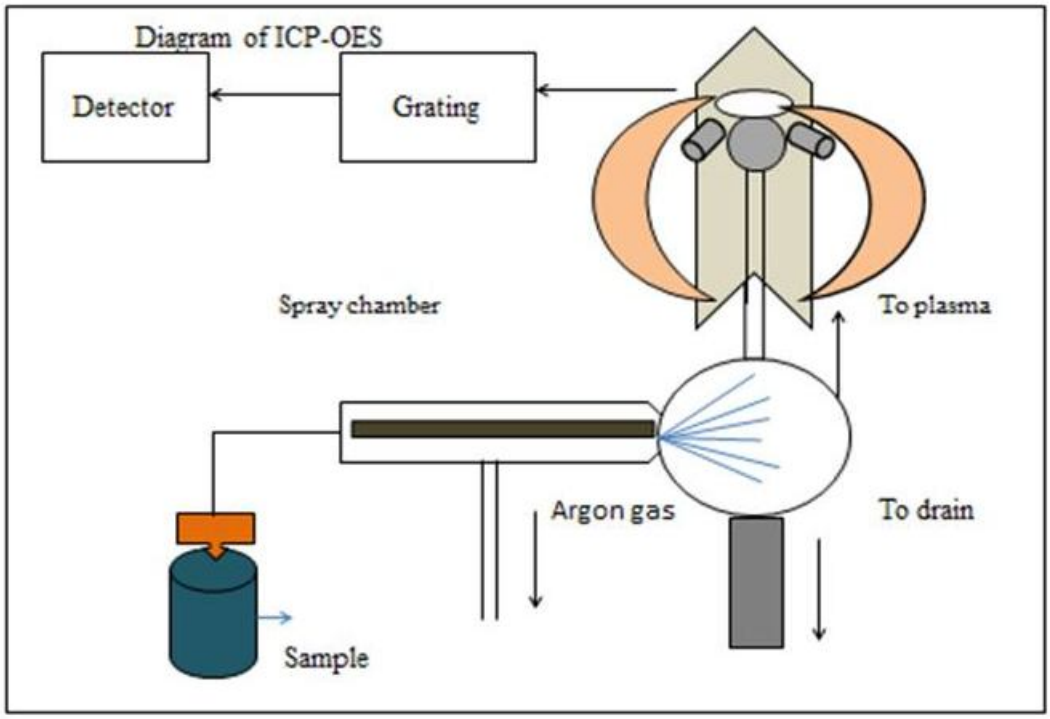

Fig. 8: Schematic diagram of ICP-OES

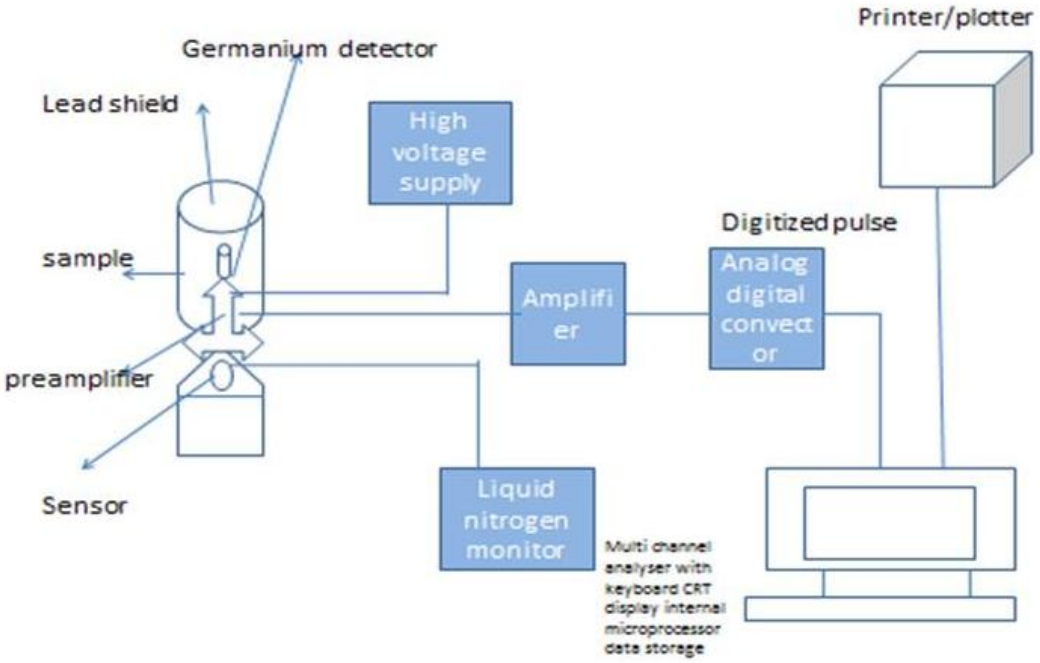

Fig. 9: Schematic diagram of INAA

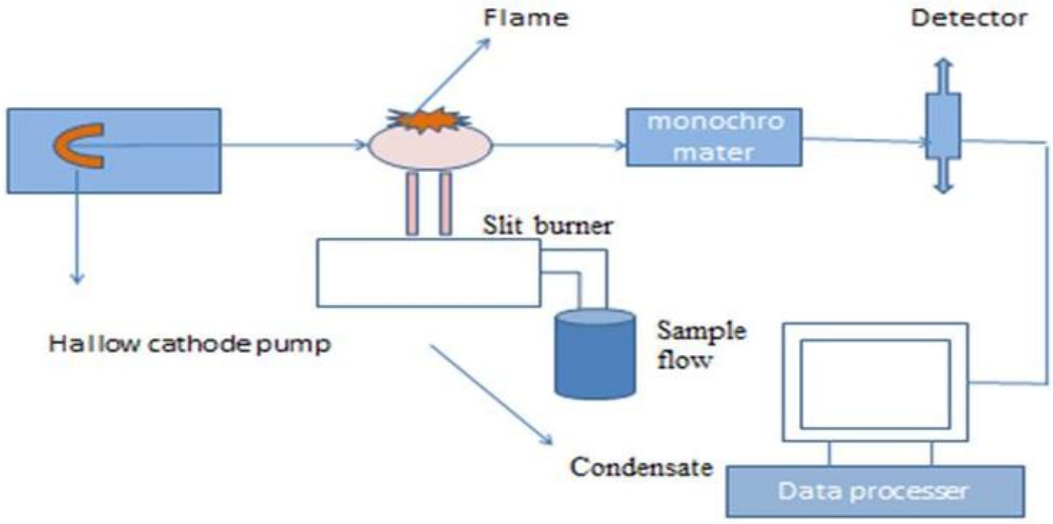

Fig. 10: Schematic diagram of AAS

7. REFERENCES

1. Balaram VJTtiAc. Recent advances in the determination of elemental impurities in pharmaceuticals–Status, challenges and moving frontiers. 2016;80:83-95.
2. Jenke DJPJoPS, Technology. Materials in Manufacturing and Packaging Systems as Sources of Elemental Impurities in Packaged Drug Products: An Updated Literature Review. 2020;74(3):324-47.
3. Pohl P, Bielawska-Pohl A, Dzimitrowicz A, Jamroz P and Welna MJTTiAC. Impact and practicability of recently introduced requirements on elemental impurities. 2018;101:43-55.
4. Li G, Schoneker D, Ulman KL, Sturm JJ, Thackery LM and Kauffman JFJJops. Elemental impurities in pharmaceutical excipients. 2015;104(12):4197-206.
5. Barin JS, Mello PA, Mesko MF, Duarte FA, Flores EMJA and chemistry b. Determination of elemental impurities in pharmaceutical products and related matrices by ICP-based methods: a review. 2016;408(17):4547-66.
6. Pereira LS, Iop GD, Flores EM, Burrow RA, Mello PA and Duarte FAJF. Strategies for the determination of trace and toxic elements in pitch: Evaluation of combustion and wet digestion methods for sample preparation. 2016;163:175-9.
7. Mesko MrF, Pereira JS, Moraes DP, Barin JS, Mello PA and Paniz JNG. Focused microwave-induced combustion: a new technique for sample digestion. 2010;82(5):2155-60.
8. Maithani M, Raturi R, Sharma P, Gupta V and Bansal PJRT. Pharmacology. Elemental impurities in pharmaceutical products adding fuel to the fire. 2019;108:104435.
9. Katakam LN and Aboul-Enein HYJCPA. Elemental Impurities Determination by ICP-AES/ICP-MS: A review of Theory, Interpretation of Concentration Limits, Analytical Method Development Challenges and Validation Criterion for Pharmaceutical Dosage Forms. 2020;16(4):392-403.
10. Al-Rashdan A, Heitkemper D and Caruso JAJJocs. Lead Speciation by HPLC—ICP—AES and HPLC ICPMS. 1991;29(3):98-102.
11. Sungur Ş and Gülmez FJJoS. Determination of metal contents of various fibers used in textile industry by MP-AES. 2015;2015.
12. Smirnova SV, Samarina TO, Ilin DV and Pletnev IVJAc. Multielement determination of trace heavy metals in water by microwave-induced plasma atomic emission spectrometry after extraction in unconventional single-salt aqueous biphasic system. 2018;90(10):6323-31.
13. Balaram VJMJ. Microwave plasma atomic emission spectrometry (MP-AES) and its applications–A critical review. 2020;105483.
14. Pluháček T, Ručka M and Maier VJACA. A direct LA-ICP-MS screening of elemental impurities in pharmaceutical products in compliance with USP and ICH-Q3D. 2019;1078:1-7.
15. Danyushevsky L, Robinson P, Gilbert S, Norman M, Large R and McGoldrick P. Routine quantitative multi-element analysis of sulphide minerals by laser ablation ICP-MS: Standard development and consideration of matrix effects. 2011;11(1):51-60.
16. Rudovica V, Viksna A, Actins AJJoP and Analysis B. Application of LA-ICP-MS as a rapid tool for analysis of elemental impurities in active pharmaceutical ingredients. 2014;91:119-22.
17. Limbeck A, Galler P, Bonta M, Bauer G, Nischkauer W and Vanhaecke FJA. Recent advances in quantitative LA-ICP-MS analysis: challenges and solutions in the life sciences and environmental chemistry. 2015;407(22):6593-617.
18. Limbeck A, Bonta M and Nischkauer WJJoAAS. Improvements in the direct analysis of advanced materials using ICP-based measurement techniques. 2017;32(2):212-32.
19. Liu Y, Hu Z, Li M and Gao SJCSB. Applications of LA-ICP-MS in the elemental analyses of geological samples. 2013;58(32):3863-78.
20. Gaudiuso R, Dell'Aglio M, Pascale OD, Senesi GS and Giacomo ADJS. Laser induced breakdown spectroscopy for elemental analysis in environmental, cultural heritage and space applications: a review of methods and results. 2010;10(8):7434-68.
21. Gaines PJS. Sample introduction for ICP-MS and ICP-OES. 2005;20(1):20-3.

22. Støving C, Jensen H, Gammelgaard B, Stürup SJJop and analysis b. Development and validation of an ICP-OES method for quantitation of elemental impurities in tablets according to coming US pharmacopeia chapters. 2013;84:209-14.
23. Pinheiro FC, Barros AI and Nóbrega JAJMJ. Evaluation of dilute-and-shoot procedure for determination of inorganic impurities in liquid pharmaceutical samples by ICP OES. 2019;146:948-56.
24. Xu N, Chamberlin RM, Thompson P, Kaye PJJoR and Chemistry N. Integrated approaches for reducing sample size for measurements of trace elemental impurities in plutonium by ICP-OES and ICP-MS. 2017;314(3):1577-85.
25. Guerin T, Astruc M, Batel A and Borsier MJT. Multielemental speciation of As, Se, Sb and Te by HPLC-ICP-MS. 1997;44(12):2201-8.
26. Chahrour O, Malone J, Collins M, Salmon V, Greenan C and Bombardier A. Development and validation of an ICP-MS method for the determination of elemental impurities in TP-6076 active pharmaceutical ingredient (API) according to USP< 232>/< 233. 2017;145:84-90.
27. Muller AL, Oliveira JS, Mello PA, Muller EI and Flores EMJT. Study and determination of elemental impurities by ICP-MS in active pharmaceutical ingredients using single reaction chamber digestion in compliance with USP requirements. 2015;136:161-9.
28. Krishna MB and Arunachalam JJT. Trace element analysis of high purity arsenic through vapour phase dissolution and ICP-QMS. 2003;59(3):485-92.
29. Wang M, Feng WY, Zhao YL and Chai ZFJMsr. ICP-MS-based strategies for protein quantification. 2010;29(2):326-48.
30. Rao RN, Talluri MKJJop and analysis b. An overview of recent applications of inductively coupled plasma-mass spectrometry (ICP-MS) in determination of inorganic impurities in drugs and pharmaceuticals. 2007;43(1):1-13.
31. Michalski R, Jabłonska M, Szopa S and Łyko AJCRiAC. Application of ion chromatography with ICP-MS or MS detection to the determination of selected halides and metal/metalloids species. 2011;41(2):133-50.
32. Godshaw J, Hopfer H, Nelson J and Ebeler SEJM. Comparison of dilution, filtration, and microwave digestion sample pretreatments in elemental profiling of wine by ICP-MS. 2017;22(10):1609.
33. Fischer L, Zipfel B, Koellensperger G, Kovac J, Bilz S and Kunkel A. Flow injection combined with ICP-MS for accurate high throughput analysis of elemental impurities in pharmaceutical products according to USP< 232>/< 233. 2014;95:121-9.
34. Pozebon D, Scheffler G and Dressler VJJoAAS. Recent applications of laser ablation inductively coupled plasma mass spectrometry (LA-ICP-MS) for biological sample analysis: a follow-up review. 2017;32(5):890-919.
35. Hall G, Bonham-Carter G, Maclaurin A and Ballantyne SJT. Comparison of instrumental neutron activation analysis of geological materials with other multielement techniques. 1990;37(1):135-55.
36. Abdel-Haleem A, Sroor A, El-Bahi S, Zohny EJAR and Isotopes. Heavy metals and rare earth elements in phosphate fertilizer components using instrumental neutron activation analysis. 2001;55(4):569-73.
37. Orvini E, Speziali M, Salvini A and Herborg CJMJ. Rare earth elements determination in environmental matrices by INAA. 2000;67(1-3):97-104.
38. Chen K-S, Tseng C-L, Lin T-HJJor and chemistry n. Trace elements in natural drugs determined by INAA. 1993;170(1):265-80.
39. Ataman OYJSAPBAS. Vapor generation and atom traps: atomic absorption spectrometry at the ng/L level. 2008;63(8):825-34.
40. Jurowski K, Krośniak M, Fołta M, Tatar B, Cole M and Piekoszewski WJJoTEiM. The toxicological analysis of Cu, Mn and Zn as elemental impurities in pharmaceutical herbal products for teething available in pharmacies in Poland. 2019;53:109-12.
41. Mattiazzi P, Bohrer D, Becker E, Viana C, Nascimento PC and Carvalho LMJT. High-resolution continuum source graphite furnace atomic absorption spectrometry for screening elemental impurities in drugs to

adhere to the new international guidelines. 2019;197:20-7.
42. Mello PA, Rodrigues LF, Nunes MA, Mattos JCP, Müller EI and Dressler VL. Determination of metal impurities in carbon nanotubes by direct solid sampling electrothermal atomic absorption spectrometry. 2011;22(6):1040-9.
43. Tavares TR, Nunes LC, Alves EEN, Almeida Ed, Maldaner LF and Krug FJ. Simplifying sample preparation for soil fertility analysis by X-ray fluorescence spectrometry. 2019;19(23):5066.
44. Arzhantsev S, Li X and Kauffman JFJAc. Rapid limit tests for metal impurities in pharmaceutical materials by X-ray fluorescence spectroscopy using wavelet transform filtering. 2011;83(3):1061-8.
45. Prange A and Schwenke HJAiX-ra. Trace element analysis using total-reflection X-ray fluorescence spectrometry. 1991;35(B):899-923.