

INDUCTIVELY COUPLED PLASMA: THE FUTURE OF HEAVY METALS TESTING

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The USP has proposed using inductively coupled plasma (ICP) for determining heavy metals in drug articles to replace the USP <231> heavy metals test. While the current USP <231> procedure will detect Pb, Hg, Bi, As, Sb, Sn, Cd, Ag, Cu and Mo, the proposed method will test for Al, Sb, As, Be, B, Cd, Cr, Co, Cu, In, Ir, Fe, Pb, Li, Mg, Mn, Hg, Mo, Ni, Os, Pd, Pt, Rh, Rb, Ru, Se, Sr, Tl, Sn, W and Zn.

The current USP heavy metals method is not specific, not sensitive enough, nor does it provide adequate recovery of the elements being tested. The proposed revision will eliminate the specificity issue, provide greater sensitivity down to part-per-billion (ppb) levels and will evaluate the drug article for an additional 21 elements.

WHAT IS ICP?

Inductively Coupled Plasma has been commercially available for over 40 years and is used to measure trace metals in a variety of solutions. ICP can be performed using various techniques, two of which are inductively coupled plasma - optical emission spectroscopy (ICP-OES) and inductively coupled plasma - mass spectrometry (ICP-MS). This discussion will focus on ICP-OES.

Sample solutions are introduced into the ICP as an aerosol that is carried into the center of the plasma (superheated inert gas). The plasma desolvates the aerosol into a solid, vaporizes the solid into a gas, and then dissociates the individual molecules into atoms. This high temperature source (plasma) excites the

atoms and ions to emit light at particular wavelengths, which correspond to different elements in the sample solution. The intensity of the emission corresponds to the concentration of the element detected.

WHAT ARE THE ADVANTAGES OF ICP OVER OTHER ANALYTICAL TECHNIQUES?

There are other instruments that have comparable limits of detection to ICP. The atomic absorption spectrometer (AAS) and graphite furnace atomic absorption spectrometer (GFAAS) can also perform trace metal analysis. However, ICP can analyze multiple elements at one time and has longer linear ranges compared to AAS and GFAAS. The linearity for ICP ranges from 4 to 6 orders of magnitude whereas AAS and GFAAS range from 2 to 3 orders of magnitude. ICP has less chemical interference than AAS or GFAAS due to the high temperature of the plasma and also has less matrix interference due to its mode of sample introduction. Furthermore, ICP has a variety of emission lines to choose from to reduce interference from other elements and to increase sensitivity.

WHY TEST FOR METALS?

Most heavy metals are toxic and should not be present in drug articles above determined exposure levels. In addition, heavy metal contaminants may potentially interact with components of associated medicines. Metal contaminants come from various sources:

- They may have been used as catalysts during production
- They may be present as contaminants in starting materials
- They may be added during the

manufacturing process from equipment. In rare instances, they may be a component of the active ingredient. Keys to ICP Testing

SAMPLE AND STANDARD PREPARATION

Sample preparation is critical to the success of the method. The sample can be dissolved in a solvent, typically a dilute acid, but water or an organic solvent may also be used. Typically dilute nitric acid or hydrochloric acid is used to eliminate interference, but other acids may be used if necessary. If the sample is not soluble or the solution clogs the nebulizer, an alternate sample preparation method is required. Acid digestion may also be used, however precaution must be taken to prevent loss of elements during the heating process.

Standards can be prepared by diluting commercially available NIST traceable standard solutions. Precautions must be taken when making mixed standard preparations to ensure all of the elements are compatible in solution and no precipitation occurs. It is important to prepare standards and blanks in the same matrix as that of the sample to eliminate interference.

On occasion, interference may occur due to the high concentration of solids in the sample solution. If matrix matching is not an option or interference still occurs, an internal standard can be used.

SAMPLE INTRODUCTION

The sample solution is introduced into the nebulizer where it is converted into an aerosol. Different nebulizers are available for different applications, such

as hydrofluoric acid, high solids content or organic solutions. Care must be taken in sample introduction as this step represents the greatest source of noise, resulting in reduced sensitivity.

INSTRUMENT CALIBRATION

Before sample analysis, the ICP must be calibrated. Calibration consists of analyzing standards and a blank within the linear range of the element being analyzed. The linear range for ICP-OES is typically 4 to 6 orders of magnitude of concentration, therefore only one or two standards may be necessary for the calibration curve. Typically a check standard is analyzed and compared to the initial standard response throughout the run.

WAVELENGTH SELECTION

If the method does not specify the exact wavelength to be used, one will need to be selected. The wavelength selected must be appropriate for the concentrations being analyzed. For example, when performing trace level

analyses, the least sensitive wavelength would not be used. When analyzing multiple elements, the wavelength(s) chosen must take into account interference from the other elements being analyzed.

SUMMARY

ICP spectroscopy offers a more sensitive, specific and reproducible way to determine heavy metal concentration in drug articles than the classic colorimetric method outlined in USP <231>. ICP has been a quality control technique long utilized by environmental, mineral, consumer product, and oil and gas industries. It is a technology that is becoming more important to the pharmaceutical industry as regulators and manufacturers continue to seek enhanced limits of detection. In February 2008, the European Medicines Agency (EMA) issued its "Guideline on the Specification Limits for Residues of Metal Catalysts or Metal Reagents". The document recommends maximum acceptable concentration limits of metal residues arising from the use of metal catalysts or metal reagents in the synthesis of drug

substances (APIs) and excipients. This new EMA guideline became effective on September 1, 2008.

ICP detection limits for most elements is in the part-per-billion (ppb) range, offering better sensitivity than the current USP <231> heavy metals test. In addition, the ability to use alternate nebulizers and wavelengths gives more flexibility to analyzing various samples. Enhanced flexibility and sensitivity also expands the utilization of the ICP beyond raw material and finished product screening. It can be a useful tool in cleaning validations and extractable and leachable studies as well.

Despite all these advantages, the cost of an ICP is much higher than the current USP <231> test. A qualified ICP will run into six figures. The cost of USP <231> is a few dollars in reagents and labor cost. For many manufacturers, it makes more sense to contract out ICP analysis, rather than invest in the cost, expertise to operate the instrument, and upkeep of the equipment. SGS has several qualified ICP's for pharmaceutical analysis. Contact us to schedule sample analysis.

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