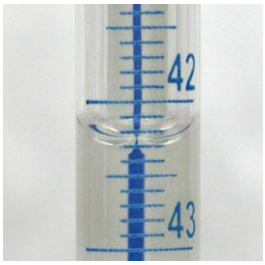
Misuse of ICP-MS and OES for Routine Assay Analysis of High Purity Salts

Jost Chemical often gets asked why assay values obtained using ICP-MS/OES do not match the reported assay values on Jost's product certificate of analysis (CoA) which utilizes compendia classical "wet" assay methods. One frequent concern that we address is an analyst reporting non-conforming assay data when practicing non-compendia methodology using Inductively Coupled Plasma Mass Spectroscopy (ICP-MS) or Inductively Coupled Plasma Optical Emission Spectroscopy (ICP-OES), both of which are intended for compendia trace elemental analysis.

Utilization of the proper analytical technique for chemical analysis is critical for accurate measurements. When analyzing a single, chemically pure compound such as calcium citrate tetrahydrate or magnesium phosphate tribasic, classical "wet" methods of assay should be used. These classical "wet" methods of analysis such as EDTA titration are used for percentage scale determinations of metal analytes. The precision of these methods is typically on the order of +/- 0.2% relative standard deviation (RSD) with accuracy approaching 100%. This high degree of precision and accuracy can be attributed to a relatively large sample size combined with minimal dilutions, typically on the order of 1X to 10X. Jost Chemical, along with the compendia monographs, always utilize classical volumetric or gravimetric methods of analysis when determining metal analyte concentrations of 0.1% or greater.



ICP methods are used for trace impurity analysis of compounds which typically are contaminations on the parts per million (ppm) to parts per billion (ppb) level.

Due to the sensitive nature of the instrumentation and detectors, sample size/solid loading must be kept extremely small to eliminate fouling. Decreasing the sample size/solid loading requires several dilutions, often approaching a factor of 2,500X. When multiple dilutions are employed, losing a fraction of a drop due to accidental loss or poor technique can have significant effect on assay results. Typically, a precision RSD of +/-5% is considered acceptable for a given sample set using ICP-MS/OES. Good accuracy only becomes apparent with multiple sample preparations and replicate runs.

ICP technology has earned its place in analytical instrumentation excellence. The forte of ICP-MS/OES technology is the ability to observe extremely small quantities of metal analytes in either a simple or complex matrix. As acceptable levels of heavy metals approach sub ppm levels (i.e. California Prop 65), only ICP-MS and ICP-OES can accurately detect and report these sub ppm levels. The ICP-MS +/-5% RSD is not detrimental to analysis at ppm levels. For example a calcium citrate analysis returns a 0.1 ppm lead level using ICP-MS/OES. With a relatively large RSD of +/-5%, the reportable lead level is still 0.1 ppm because values between 0.095 and 0.105 ppm lead would be reported by the instrument.

Another example of acceptable ICP-MS/OES use is analysis of formulation blends that contain more than one metal analyte in a sample matrix. EDTA titration would not be a preferred method of determination due

to lack of specificity. It is well known that ICP-MS and ICP-OES are outstanding choices for detection and quantification of multiple metal analytes within a complex formulation matrix. With that being said, formulators typically charge roughly 110% of the required minimum dosage for each required metal. Using ICP-MS/OES analysis, formulators will typically see assay values for their metal between 105% - 115% (+/-5% RSD of metal charged). This coincidentally guarantees passing the minimum required label content, not because of ICP-MS/OES precision, but because the lowest assay value possible is still above the label claim minimum due to the "overcharge" of raw materials into the formulation.

Supplement Facts
Serving Size: 1 Tablet

Amount Per Serving		% DV
Vitamin A (as Acetate & 20% as Beta Carotene)	3,500 I.U.	70%
Vitamin C (as Ascorbic Acid)	60 mg	100%
Vitamin D (as Cholecalciferol)	400 I.U.	100%
Vitamin E (as d-alpha Tocopheryl Acetate)	45 I.U.	150%
Vitamin K (as Phytonadione)	10 mcg	12%
Thiamin (Thiamin Mononitrate, B1)	1.5 mg	100%
Riboflavin (Vitamin B2)	1.7 mg	100%
Niacin (as Niacinamide)	20 mg	100%
Vitamin B6 (as Pyridoxine HCl)	3 mg	150%
Folic Acid	400 mcg	100%
Vitamin B12 (as Cyanocobalamin)	25 mcg	417%
Biotin	30 mcg	10%
Pantothenic Acid (as d-Calcium Pantothenate)	10 mg	100%
Calcium (as Calcium Phosphate & Carbonate)	200 mg	20%
Phosphorus (as Calcium Phosphate)	48 mg	5%
Iodine (as Potassium Iodide)	150 mcg	100%
Magnesium (as Magnesium Oxide)	100 mg	25%
Zinc (as Zinc Oxide)	15 mg	100%
Selenium (as Sodium Selenate)	20 mcg	29%
Copper (as Cupric Oxide)	2 mg	100%
Manganese (as Manganese Sulfate)	2 mg	100%
Chromium (as Chromium Chloride)	150 mcg	125%
Molybdenum (as Sodium Molybdate)	75 mcg	100%
Chloride (as Potassium Chloride)	72 mg	2%
Potassium (as Potassium Chloride)	80 mg	2%
Boron (as Borates)	150 mcg	**
Nickel (as Nickelous Sulfate)	5 mcg	**
Silicon (as Silicon Dioxide)	2 mg	**
Vanadium (as Sodium Metavanadate)	10 mcg	**
Lycopene	300 mcg	**
Lutein	250 mcg	**

** Daily Value (DV) not established.

Other Ingredients: Cellulose, Starch, Croscarmellose Sodium, Stearic Acid, Silicon Dioxide, Titanium Dioxide, Magnesium Stearate, Artificial Colors (FD &C Blue #2, FD&C Yellow #6, FD&C Red #40). 0105

Typically, acceptable compendia monograph assay ranges are between 98 – 101.5% which gives a range of roughly +/- 2% from theoretical 100%. Using Jost Chemical's Magnesium Phosphate Tribasic as an example, I will show the effect each assay method can have on the true assay value. Theoretically, the assay for 100% fully reacted material should be 20.7% magnesium (Mg) and have an acceptable USP Mg assay range of 20.2 – 20.9%. Using classic EDTA titrations, with the aforementioned +/-0.2% RSD, one would expect to consistently achieve Mg assays in the 20.6 – 20.8% range, which is well within the acceptable USP target range of 20.2-20.9% Mg. However, if ICP analysis is employed with the aforementioned +/-5% RSD, one could reliably only expect Mg assays in the 19.7 – 21.7% range, which extends both above and below the acceptable USP target range shown above. This can lead to product rejection or failure due to imprecision of ICP-MS/OES at high levels (>0.1%) of metal analyte analysis, not chemical purity.

There are compendia precedents that clearly establish the specific compendia assay methods as the final arbitrator of any disputed result. The FCC 9th Edition, p2, "Alternative Analytical Procedures" states…

> *"Although the tests and assays described constitute procedures upon which the specifications of the FCC depend, analysts are not prevented from applying alternative procedures if supporting data shows that the procedures used will produce results of equal or greater accuracy. In the event of the doubt or disagreement concerning a substance purported to comply with the specifications of the FCC, only the methods described herein are applicable and authoritative."*

The USP 39, section 5.5, "Assay" also supports this dispute resolution via…

> *"Assay tests for compounded preparations are not intended for evaluating a compounded preparation before dispensing, but are intended to serve as the official test in the event of a question or dispute regarding the preparation's conformance to official standards."*

If you need further assistance, please do not hesitate to contact Jost Chemical Company for any additional information you may need.