to within ±20% for multi-element analyses, or when concentrations are <1 ng per mL. In cases where an individual monograph provides different guidance regarding the reassayed check standard, the requirements of the monograph take precedence.

The method of standard additions should be employed in situations where matrix interferences are expected or suspected. This method involves adding a known concentration of the analyte element to the sample solution at no fewer than two concentration levels. The instrument response is plotted against the concentration of the added analyte element, and a linear regression line is drawn through the data points. The absolute value of the x-intercept multiplied by any dilution factor is the concentration of the analyte in the sample.

Procedure

Follow the procedure as directed in the individual monograph for the detection mode and instrument parameters. The specification of definitive parameters in a monograph does not preclude the use of other suitable operating conditions, and adjustments of operating conditions may be necessary. Alternative conditions must be supported by suitable validation data, and the conditions in the monograph will take precedence for official purposes. Because of differences in manufacturers' equipment configurations, the analyst may wish to begin with the manufacturer's suggested default conditions and modify them as needed. Data collected from a single sample introduction are treated as a single result. Data collected from replicate sequential readings from a single introduction of the appropriate standard or sample solutions are averaged as a single result. Sample concentrations are calculated versus the working curve generated by plotting the detector response versus the concentration of the analyte in the standard solutions. With modern instruments, this calculation is often performed by the instrument.

GLOSSARY

AUXILIARY GAS: See *Intermediate (or Auxiliary) Gas.*

AXIAL VIEWING: A configuration of the plasma for AES in which the plasma is directed toward the spectrometer optical path, also called "end-on viewing."

CENTRAL (OR NEBULIZER) GAS: One of three argon gas flows in an ICP torch. The central gas is used to help create a fine mist of the sample solution when solution nebulization is employed. This fine mist is then directed through the central tube of the torch and into the plasma.

COLLISION CELL: A design feature of some ICP–MS instruments. Collision cells are used to reduce interferences from argon species or polyatomic ions and facilitate the analysis of elements that might be affected by those interferences.

COOL PLASMA: Plasma conditions used for ICP–MS that result in a plasma that is cooler than that normally used for an analysis. This condition is achieved by using a lower forward power setting and higher central-gas flow rate, and is used to help reduce isotopic interferences caused by argon and some polyatomic ions.

COOLANT GAS: See *Outer (or Coolant or Plasma) Gas.*

FORWARD POWER: The number of watts used to ignite and sustain the plasma during an analysis. Forward power requirements may vary, depending on sample matrix and analyte.

INTERMEDIATE (OR AUXILIARY) GAS: Gas used to "lift" the plasma off the surface of the torch, thereby preventing melting of the intermediate tube and the formation of carbon and salt deposits on the inner tube.

INTERNAL STANDARD: An element added to or present in the same concentration in blanks, standards, and samples to act as an intensity reference for the analysis. An internal standard should be used for ICP–AES work and must always be used for quantitative ICP–MS analyses.

LATERAL VIEWING: See *Radial Viewing.*

m: The ion mass of interest.

MULTIPLY-CHARGED IONS: Atoms that, when subjected to the high-ionization temperature of the ICP, can form doubly or triply charged ions (X^{++}, X^{+++}, etc.). When detected by MS, the apparent mass of these ions will be $^1/_2$ or $^1/_3$ that of the atomic mass.

NEBULIZER: Used to form a consistent sample aerosol that mixes with the argon gas, which is subsequently sent into the ICP.

OUTER (OR COOLANT OR PLASMA) GAS: The main gas supply for the plasma.

PLASMA GAS: See *Outer (or Coolant or Plasma) Gas.*

RADIAL VIEWING: A configuration of the plasma for AES in which the plasma is viewed orthogonal to the spectrometer optic path. Also called "side-on viewing." See also *Lateral Viewing.*

REACTION CELL: Similar to *Collision Cell,* but operating on a different principle. Designed to reduce or eliminate spectral interferences.

SAMPLING CONE: A metal cone (usually nickel-, aluminum-, or platinum-tipped) with a small opening, through which ionized sample material flows after leaving the plasma.

SEQUENTIAL: A type of detector configuration for AES or MS in which discrete emission lines or isotopic peaks are observed by scanning or hopping across the spectral range by means of a monochromator or scanning mass spectrometer.

SIMULTANEOUS: A type of detector configuration for AES or MS in which all selected emission lines or isotopic peaks are observed at the same time by using a polychromator or simultaneous mass spectrometer, offering increased analysis speed for analyses of multi-element samples.

SKIMMER CONE: A metal cone through which ionized sample flows after leaving the sampling cone and before entering the high-vacuum region of an ICP–MS.

STANDARD ADDITIONS: A method used to determine the actual analyte concentration in a sample when viscosity or matrix effects might cause erroneous results.

TORCH: A series of three concentric tubes, usually manufactured from quartz, in which the ICP is formed.

⟨731⟩ LOSS ON DRYING

The procedure set forth in this chapter determines the amount of volatile matter of any kind that is driven off under the conditions specified. For substances appearing to contain water as the only volatile constituent, the procedure given in the chapter, *Water Determination* ⟨921⟩, is appropriate, and is specified in the individual monograph.

Unless otherwise directed in the individual monograph, conduct the determination on a 1 to 2 g test specimen. Mix the substance to be tested and, if it is in the form of large particles, reduce the particle size to about 2 mm by quickly crushing before weighing out the test specimen. Tare an appropriate glass-stoppered, shallow weighing bottle that has been dried for about 30 minutes under the same conditions to be employed in the determination and cooled to room temperature in a desiccator. Put the test specimen in the bottle, replace the cover, and accurately weigh the bottle and the contents. By gentle, sidewise shaking, distribute the test specimen as evenly as practicable to a depth of about 5 mm generally, and not more than 10 mm in the

case of bulky materials. Place the loaded bottle in the drying chamber, removing the stopper and leaving it also in the chamber. Dry the test specimen at the temperature and for the time specified in the monograph. [NOTE—The temperature specified in the monograph is to be regarded as being within the range of ±2° of the stated figure.] Upon opening the chamber, close the bottle promptly, and allow it to come to room temperature in a desiccator before weighing.

If the substance melts at a lower temperature than that specified for the determination of *Loss on drying*, maintain the bottle with its contents for 1 to 2 hours at a temperature 5° to 10° below the melting temperature, then dry at the specified temperature.

Where Capsules are to be tested, use a portion of the mixed contents of not fewer than 4 capsules.

Where Tablets are to be tested, use powder from not fewer than 4 tablets.

Where the individual monograph directs that loss on drying be determined by thermogravimetric analysis, a sensitive electrobalance is to be used.

Where drying in vacuum over a desiccant is directed in the individual monograph, a vacuum desiccator or a vacuum drying pistol, or other suitable vacuum drying apparatus, is to be used.

Where drying in a desiccator is specified, exercise particular care to ensure that the desiccant is kept fully effective by frequent replacement.

Where drying in a capillary-stoppered bottle* in vacuum is directed in the individual monograph, use a bottle or tube fitted with a stopper having a 225 ± 25 µm diameter capillary, and maintain the heating chamber at a pressure of 5 mm or less of mercury. At the end of the heating period, admit dry air to the heating chamber, remove the bottle, and with the capillary stopper still in place allow it to cool to room temperature in a desiccator before weighing.

⟨733⟩ LOSS ON IGNITION

This procedure is provided for the purpose of determining the percentage of test material that is volatilized and driven off under the conditions specified. The procedure, as generally applied, is nondestructive to the substance under test; however, the substance may be converted to another form such as an anhydride.

Perform the test on finely powdered material, and break up lumps, if necessary, with the aid of a mortar and pestle before weighing the specimen. Weigh the specimen to be tested without further treatment, unless a preliminary drying at a lower temperature, or other special pretreatment, is specified in the individual monograph. Unless other equipment is designated in the individual monograph, conduct the ignition in a suitable muffle furnace or oven that is capable of maintaining a temperature within 25° of that required for the test, and use a suitable crucible, complete with cover, previously ignited for 1 hour at the temperature specified for the test, cooled in a desiccator, and accurately weighed.

Unless otherwise directed in the individual monograph, transfer to the tared crucible an accurately weighed quantity, in g, of the substance to be tested, about equal to that calculated by the formula:

$$10/L$$

in which L is the limit (or the mean value of the limits) for *Loss on ignition*, in percentage. Ignite the loaded uncovered crucible, and cover at the temperature (±25°) and for the period of time designated in the individual monograph. Ignite for successive 1-hour periods where ignition to constant weight is indicated. Upon completion of each ignition, cover the crucible, and allow it to cool in a desiccator to room temperature before weighing.

*Available as an "antibiotic moisture content flask" from Kimble- Kontes, 1022 Spruce St., Vineland, NJ 08362-1502.

⟨736⟩ MASS SPECTROMETRY

A mass spectrometer produces ions from the substance under investigation, separates them according to their mass-to-charge ratio (m/z), and records the relative abundance of each ionic species present. The instrument consists of three major components (see *Figure 1*):

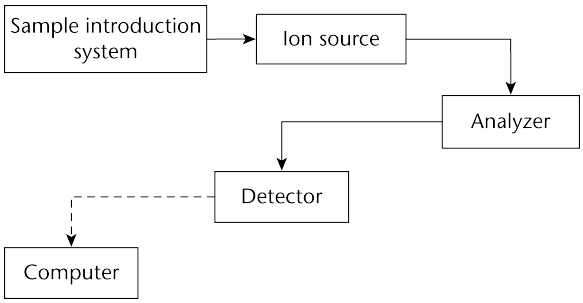

Figure 1. Major components of a mass spectrometer.

an ion source for producing gaseous ions from the substance being studied, an analyzer for resolving the ions into their characteristic mass components according to their mass-to-charge ratios, and a detector system for detecting the ions and recording the relative abundance of each of the resolved ionic species. In addition, a sample introduction system is necessary to admit the samples to be studied to the ion source while maintaining the high vacuum requirements (~10^{-6} to 10^{-8} mm of mercury) of the technique; and a computer is required to control the instrument, acquire and manipulate data, and compare spectra to reference libraries.

This chapter gives an overview of the theory, construction, and use of mass spectrometers. The discussion is limited to those instruments and measurements with actual or potential application to compendial and other pharmaceutical requirements: generally, the identification and quantitation of specific compounds.

SAMPLE INTRODUCTION

Samples are introduced either as a gas to be ionized in the ion source, or by ejection of charged molecular species from a solid surface or solution. In some cases sample introduction and ionization take place in a single process, making a distinction between them somewhat artificial.

Substances that are gases or liquids at room temperature and atmospheric pressure can be admitted to the source as a neutral beam via a controllable leak system. Volatilizable compounds dissolved or adsorbed in solids or liquids can be removed and concentrated with a headspace analyzer. Vapors are flushed from the solid or liquid matrix with a stream of carrier gas and trapped on an adsorbing column. The trapped vapors are subsequently desorbed by programmed heating of the trap and introduced into the mass spectrometer by a capillary connection.