6 Atomic spectrophotometry

Atomic emission spectrophotometry (AES)

KEYPOINTS

Principles

Atoms are thermally excited so that they emit light and the radiation emitted is measured.

Applications in pharmaceutical analysis

- Quantification of alkali metals in: alkali metal salts, infusion and dialysis solutions.
- Determination of metallic impurities in some of the other inorganic salts used in preparing these solutions.

Strengths

- Flame photometry provides a robust, cheap and selective method based on relatively simple instrumentation for quantitative analysis of some metals.

Limitations

- Only applicable to the determination of alkali and some alkaline earth metals.

Introduction

Atomic emission spectroscopy plays an important role in the control of sodium, potassium and lithium in a number of raw materials and formulations.

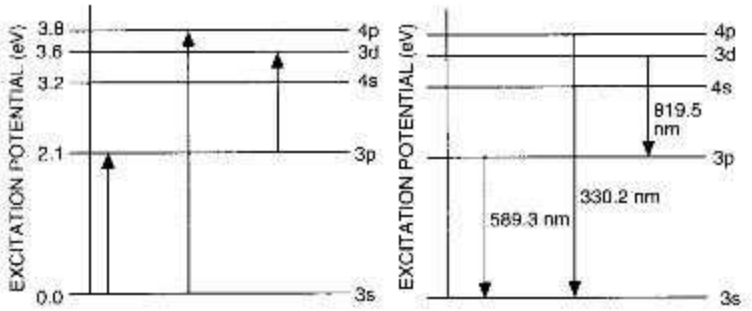

Fig. 6.1
Electronic transitions within a sodium atom giving rise to the main bands in its emission spectrum.

Atoms contain various energy states as illustrated in Figure 6.1 for the sodium atom. The normal unexcited state is the ground state. Sodium contains 1 electron in its outer ($3p$) orbital and if energy is gained by the atom this electron may be excited to a higher state and then subsequently lose its excess energy by falling back to a lower energy orbital. Thus when a sodium salt is heated in a flame the outer electrons in the volatilised atoms are excited and then return to the ground state with emission of energy, which appears for example as yellow light (wavelength 589.3 nm). The major line in the sodium emission spectrum is due to an electron falling from the $3p$ excited state to the $3s$ ground state; the atomic emission spectrum of sodium contains two other major lines at 819.5 nm and 330.2 nm due to the transitions shown in Figure 6.1. Atomic emission lines are very narrow (< 0.01 nm). Only a limited number of elements are sufficiently excited by thermal energy for AES measurements to be carried out. Common elements with emission lines suitable for utilisation in their quantitation are Ca, Ba, Na, Li and K.

Instrumentation

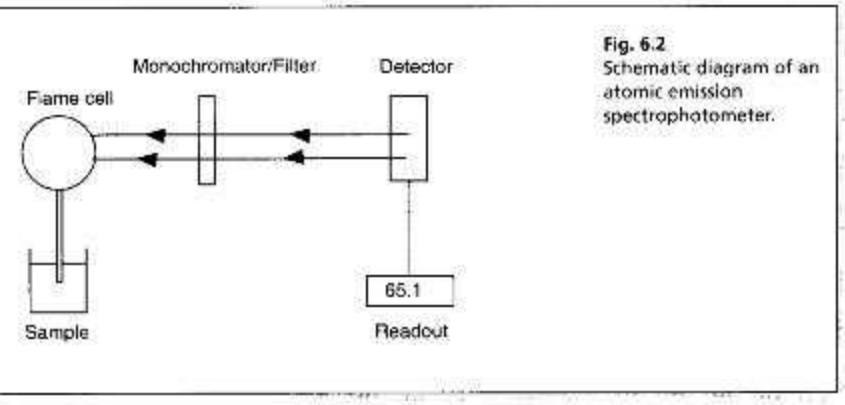

Fig. 6.2
Schematic diagram of an atomic emission spectrophotometer.

An atomic emission spectrophotometer (Fig. 6.2) is composed of the following components:

(i) **Flame.** The sample containing the metal is volatilised in a natural gas flame at 2000°C. A higher temperature (2500°C) may be obtained using air/acetylene and is required for analysis of Mg by AES.

(ii) **Monochromator/Filter.** The radiation emitted by the excited atoms is passed through a filter or a monochromator in more expensive instruments. Thus a narrow band of emitted radiation is selected and interfering sources of radiation such as the flame and other components in the sample are screened out.

(iii) **Detector.** The intensity of the selected radiation is then measured using a photosensitive cell.

Examples of quantitation by AES

In order to measure a sample by AES a calibration curve is constructed by aspirating solutions of known concentration into the flame.

Assay of sodium and potassium ions in an i.v. infusion

Standard solutions of sodium chloride (NaCl) and potassium chloride (KCl) in water were prepared and diluted appropriately to give a calibration curve across the working range across the range of the instrument (*ca* 0.05–1 mg/100 ml). The assay was then carried out by diluting the infusion until its concentration was close to that at the mid-point of the calibration series. Water is used as a blank. The following results were obtained:

(i)
- Weight of NaCl used to prepare standard solution = 0.5092 g
- Weight of KCl used to prepare standard solution = 0.1691 g

Both standards were transferred to the same 1000 ml volumetric flask and diluted to 1000 ml.

(ii) Dilutions were carried out on standards:
- *Step 1*: 20 ml of the standard solution was transferred to a 100 ml volumetric flask and was diluted to 100 ml (diluted standard solution)
- *Step 2*: A calibration series was prepared by transferring the following volumes of diluted standard solutions to 100 ml volumetric flasks 0, 5, 10, 15 and 25 ml.

(iii) The infusion solution was diluted as follows:
- *Step 1*: 5 ml to 250 ml
- *Step 2*: 10 ml to 100 ml.

(iv) The instrument was used with a sodium filter to establish the sodium calibration curve and then the sodium in the sample. The instrument was switched to a potassium filter in order to determine the potassium calibration curve and the potassium in the sample. Table 6.1 shows the readings obtained for sodium (Na) and potassium (K) in the calibration solutions as well as the concentrations of Na and K in the calibration solutions (calculated below). Calculate the concentrations of Na and K in the infusion solution in mmoles/l. Atomic weights: Na = 23; K= 39.1; Cl = 35.5.

Table 6.1 Data used in Calculation example 6.1

Amount of Na mg/100 ml	Flame photometry reading	Amount of K mg/100 ml	Flame photometry reading
0	0	0	0
0.2002	20.7	0.08923	22.4
0.4004	41.0	0.1785	41.2
0.6006	60.6	0.2677	61.2
0.8008	80.3	0.3569	80.3
1.010	100	0.4462	100

Calculation example 6.1

0.5092 g of NaCl/l is equivalent to $0.5092 \times \frac{23}{58.5} = 0.2002$ g of Na/l = 200.2 mg/l.

= 20.02 mg/100 ml.

0.1691 g of KCl is equivalent to $0.1691 \times \frac{39.1}{74.1} = 0.08923$ g of K/l = 89.23 mg/l.

= 8.923 mg/100 ml.

Dilutions of standards

Step 1: 20 to 100 ml (× 5).
Step 2: Point 1 = 5 to 100 (× 20).
Total dilution = 5 × 20 = 100.

Concentrations in solution used for point 1.

$$Na = \frac{20.02}{100} = 0.2002 \text{ mg/100 ml} \quad K = \frac{8.923}{100} = 0.08923 \text{ mg/100 ml.}$$

The rest of the points in the calibration series are simply × 2, × 3, × 4 and × 5. These values give the concentrations in Table 6.1.

The equations of the lines obtained for the above data were:

For Na y = 99.0 × +0.722.
For K y = 222 × +1.3.

Reading of diluted sample for Na = 70.2 Reading of diluted sample for K = 70.6.

Dilution of sample

Step 1: 5 to 250 ml (× 50).
Step 2: 10 ml to 100 ml (× 10) Total dilution 50 × 10 = 500.

Concentration of Na in infusion

Substituting into the equation of the line for Na.

$$\text{Concentration of Na in diluted sample} = \frac{70.2 - 0.772}{99.0} = 0.701 \text{ mg/100 ml.}$$

Dilution factor = × 500.

Concentration of Na in infusion = 0.701 × 500 = 351 mg/100 ml = 3510 mg/l.

$$= \frac{3510}{23} = 153 \text{ mmoles/l.}$$

Self-test 6.1

From the data given in Calculation example 6.1, calculate the concentration of K in the infusion.

Answer: 39.9 mmoles/l

Self-test 6.2

From the following data calculate the potassium content per tablet in effervescent KCl bicarbonate tablets.

- Weight of 20 tablets = 35.6751 g
- Weight of tablet powder taken for assay = 0.1338 g

The sample is dissolved in 500 ml of water and then 5 ml of the sample solution are taken and diluted to 100 ml.

- Weight of KCl used to prepare standard = 0.1912 g

The standard was dissolved in 100 ml of water and 5 ml of the standard solution were diluted to 250 ml.

The diluted standard solution was used to prepare a calibration series by transferring 0, 5, 10, 15, 20 and 25 ml to 100 ml volumetric flasks and making up to volume.

The following readings were obtained for the calibration series: 0, 20.3, 40.1, 60.3, 80.1 and 100.

- Reading obtained for potassium in the diluted sample solution = 73.9.

Answer: (From a computer fitted calibration curve) K 496.2 mg per tablet

Interferences in AES analysis

Ionisation

At high flame temperatures, atoms such as K may completely lose an electron thus reducing the observed emission from the sample:

$$K \underset{+e}{\overset{-e}{\rightleftharpoons}} K^{+}$$

Ionisation is an equilibrium and may be shifted to the left by addition of another readily ionised element to the sample which produces electrons. The emission lines from the added metal are unlikely to interfere because AE lines are very narrow, and thus there will be no overlap, e.g. strontium chloride solution is added in order to suppress the ionisation of K in the BP assay of effervescent KCl tablets.

Viscosity

Organic substances in a sample can either increase of decrease the rate at which it is drawn into the flame relative to a standard solution by increasing or decreasing the viscosity, e.g. sucrose decreases the rate thus giving a false low reading while ethanol increases the rate thus giving a false high reading.

Anionic interference

Anions such as sulphate and phosphate form involatile salts with metal ions and reduce the reading of the sample solution. These anions may be removed by the addition of lanthanum chloride which precipitates them out and replaces them with the chloride anion.

Assays based on method of standard additions

The method of standard additions can be used with many analytical techniques where interference from the matrix has to be eliminated and is of general use in residue or trace analysis. Essentially the technique involves addition of increasing volumes of a standard solution to a fixed volume of the sample to form a calibration series. An advantage of the technique is that since several aliquots of sample are analysed in order to produce the calibration series the method gives a measure of the

precision of the assay. For example five identical aliquots of sample solution are mixed with increasing volumes of a standard solution. If x is the amount of metal ion in the sample solution the amounts of metal ion added should be *ca* 0, 0.5x, 1.5x, 2.0x and 2.5x. The calibration curve obtained will look something like that shown in Figure 6.3. The concentration of the metal in the sample is given by the distance between the origin and where the graph intersects the x axis, i.e. the point where $Y = 0$ in the equation of the line.

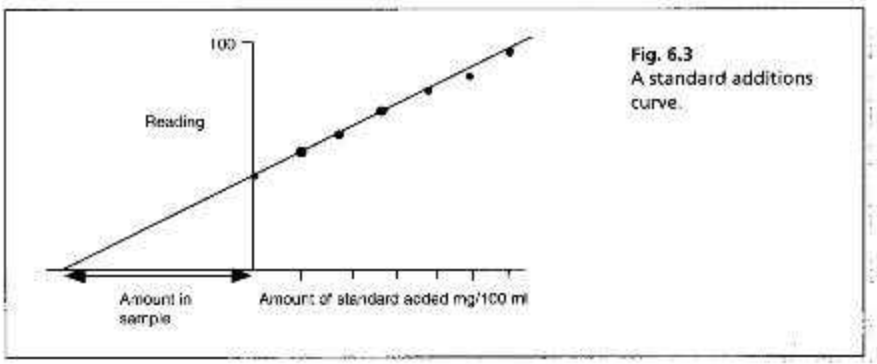

Fig. 6.3
A standard additions curve.

Assay for KCl, NaCl and glucose i.v. infusion

Analysis of the infusion was carried out using the method of standard additions, and the below data was obtained. From the tabulated data given below plot a curve and determine percentage of w/v of NaCl and KCl in the infusion.

(i) The following standard stock solutions were prepared in order to calibrate the instrument for sodium and potassium:
- NaCl (0.2351 g) was dissolved in de-ionised water and the solution was made up to 1000 ml.
- KCl (0.3114 g) was dissolved in de-ionised water and the solution was made up to 1000 ml.

(ii) An aliquot (20 ml) of each stock solution was transferred to the same 100 ml volumetric flask and the volume was adjusted to 100 ml with de-ionised water (diluted stock solution).

(iii) The sample of i.v. infusion was diluted by transferring 5 ml to a 100 ml volumetric flask and making up to volume with de-ionised water.

(iv) A calibration curve was prepared by transferring, in each case, 5 ml of diluted sample solution plus varying amounts of diluted stock solution to a 100 ml volumetric flask as indicated in Table 6.2 and then making up to 100 ml with de-ionised water.

Table 6.2 Results obtained from additions of Na and K

Volume of sample solution added	Volume of diluted stock solution added	Final volume	Reading of Na	Reading for K
5	0	100	26.1	30.1
5	5	100	39.3	45.2
5	10	100	54.2	58.8
5	15	100	69.2	73.1
5	20	100	84.1	87.0
5	25	100	100	100

Calculation example 6.2

Dilutions of standards

Initial concentration of NaCl = 0.2531 g/l = 253.1 mg/l = 25.31 mg/100 ml.

Dilution 1: 20 to 100 ml (× 5).

Dilution 2: Point 1 on calibration curve = 5 to 100 ml (× 20).

Total dilution = 5 × 20 = 100.

Concentrations in solution used for point 1.

$$\text{NaCl} = \frac{25.31}{100} = 0.2531 \text{ mg/100 ml.}$$

The rest of the points are simply × 2, × 3, × 4 and × 5, this value giving the following concentrations of added NaCl in the calibration series: 0.2531, 0.5062, 0.7593, 1.012 and 1.266 mg/100 ml.

The data were used to plot a calibration curve for NaCl.

Equation of line obtained for NaCl: $y = 58.57x + 25.09$.

When y = 0 the negative x value = concentration of NaCl in the diluted sample.

$$\text{Concentration of NaCl in diluted sample} = \frac{25.09}{58.57} = 0.4284 \text{ mg/100 ml.}$$

Dilutions of sample were 5 to 100 ml (× 20) then 5 to 100 ml (× 20) = × 400.

Concentration of NaCl in sample = 171.4 mg/100 ml = 0.1714 g/100 ml = 0.1714% w/v.

Self-test 6.3

From the data given above calculate the percentage of w/v of KCl in the sample.

Answer: from computer fitting of calibration curve KCl = 0.2742% w/v

AES is used in pharmacopoeial assays of: (1) Na in albumin solution and plasma protein solution; (2) K, Na and barium (Ba) in calcium acetate used to prepare dialysis solutions; (3) Ca in adsorbed vaccines (e.g. diphtheria and tetanus). It is also used to determine sodium and potassium concentrations in urine.

Atomic absorption spectrophotometry (AAS)

KEYPOINTS

Principles

Atoms of a metal are volatilised in a flame and their absorption of a narrow band of radiation produced by a hollow cathode lamp, coated with the particular metal being determined, is measured.

Applications in pharmaceutical analysis

- Determination of metal residues in drugs remaining from the manufacturing process.

Strengths

- More sensitive than AES. A highly specific method of analysis useful in some aspects of quality control.

Limitations

- Only applicable to metallic elements.
- Each element requires a different hollow cathode lamp for its determination.

Introduction

For many atoms the energy difference between their ground state orbital and the excited state is too great for thermal excitation of a significant number of electrons to take place. Where energy differences are too great to get an emission reading, AAS may be used. Metal atoms are volatilised in a flame and radiation is passed through the flame. In this case the volatilised atoms, which are mainly in their ground state and thus not emitting energy, will absorb radiation with an energy corresponding to the difference between their ground state and the excited state (Fig. 6.4). The number of atoms in the ground state which are available for excitation is much greater than the small fraction that become excited and emit energy in AES. Thus AAS is a much more sensitive technique than AES. Since the width of absorption or emission lines in atomic spectra is extremely narrow, the only source of light where significant absorption can be observed, after it passes through the sample, is where the light is produced by excitation of the atoms of the element being analysed. The lamp used is called a 'hollow cathode lamp' and the cathode is coated with the metal which is to be analysed. For example in the analysis of zinc (Zn), a Zn-coated cathode is used and the excitation of the Zn atoms produces a narrow band of radiation at 214 nm, which can be efficiently absorbed by the atoms in the flame. The disadvantage of this is that the lamp has to be changed every time a different element is being analysed and only one element can be analysed at a time. Modern instruments have about 12 lamps mounted on a carousel, which may be automatically rotated into line with the flame and improve the speed of multi-element analyses. Further information on the technique can be found in the additional reading.

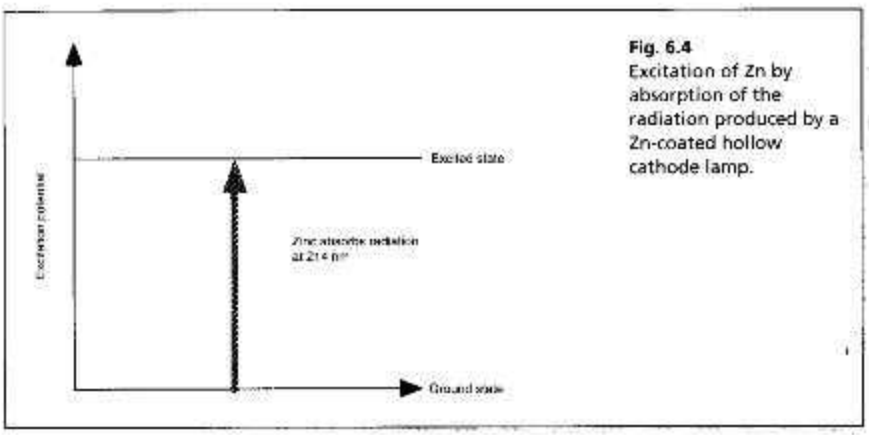

Fig. 6.4
Excitation of Zn by absorption of the radiation produced by a Zn-coated hollow cathode lamp.

Instrumentation

An atomic absorption spectrophotometer (Fig. 6.5) consists of the following components:

(i) *Light source*. A hollow cathode lamp coated with the element being analysed.
(ii) *Flame*. The flame is usually air/acetylene providing a temperature *ca* 2500°C. Nitrous oxide/acetylene may be used to produce temperatures up to 3000°C, which are required to volatilise salts of elements such as aluminium or calcium.
(iii) *Monochromator*. The monochromator is used to narrow down the width of the band of radiation being examined and is thus set to monitor the wavelength being emitted by the hollow cathode lamp. This cuts out interference by

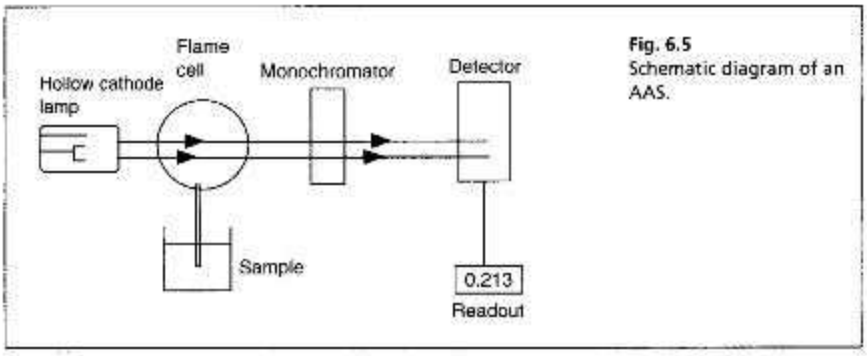

Fig. 6.5
Schematic diagram of an AAS.

radiation emitted from the flame, from the filler gas in the hollow cathode lamp and from other elements in the sample.

(iv) *Detector*. The detector is a photosensitive cell.

Examples of assays using AAS

AAS is used principally in limit tests for metals in drugs prior to their incorporation into formulations. The sample is generally dissolved in 0.1 M nitric acid to avoid formation of metal hydroxides from heavy metals, which are relatively involatile and suppress the AAS reading.

Assay of calcium and magnesium in haemodialysis fluid

The calcium (Ca) and magnesium (Mg) in a haemodialysis solution were analysed using atomic absorption spectrophotometry as follows:

(i) Standard solutions containing Ca at a concentration of 10.7 mg/100 ml of water and containing Mg at a concentration of 11.4 mg/100 ml of water were diluted as follows.

(ii) Dilution: 10 ml of both solutions were transferred to the same 100 ml volumetric flask and diluted to 100 ml (diluted standard solution).

(iii) The calibration series was prepared by diluting the diluted standard solution with water as indicated in Table 6.3.

Table 6.3 Data obtained from assay of Ca and Mg by AAS

Volume taken for dilution (ml)	Final volume (ml)	Readings for Ca dilution series	Readings for Mg dilution series
0	100	0.002	0.005
5	100	0.154	0.168
10	100	0.310	0.341
15	100	0.379	0.519
20	100	0.619	0.685
25	100	0.772	0.835

Note:

- The dialysis solution was diluted from 5 to 250 ml before analysis of Ca
- Atomic absorption reading obtained for Ca = 0.343
- The dialysis solution was diluted from 10 to 100 ml before analysis of Mg
- Atomic absorption reading obtained for Mg = 0.554
- Ca atomic weight = 40
- Mg atomic weight = 24
- Calculate the concentration of Ca in the dialysis solution in mmol l^{-1}.

Calculation example 6.3

Concentration of Ca standard solution = 10.7 mg/100 ml.

Initially both solutions were diluted 10 to 100 ml (× 10).

Thus the concentration of Ca in the diluted standard solution = 1.07 mg/100 ml.

For point 2 on the calibration curve, 5 ml of the diluted standard solution were diluted to 100 ml (× 20).

Concentration of Ca used for point 2 = $\frac{1.07}{20}$ = 0.0535 mg/100 ml.

Points 3, 4, 5 and 6 are × 2, × 3, × 4 and × 5, this value giving the following concentrations: 0.107, 0.165, 0.2140 and 0.2675 mg/100 ml.

In conjunction with the absorption readings these values were used to plot a calibration curve for Ca.

The equation obtained for the calibration line was:
y = 2.664 x – 0.007.

Reading for Ca in the diluted dialysis solution = 0.343.

From the equation for the calibration line the concentration of Ca in the diluted dialysis solution = 0.1314 mg/100 ml.

The dialysis solution was diluted 5 to 250 ml (× 50) for Ca analysis.

Therefore concentration of Ca in the undiluted dialysis solution =

6.57 mg/100 ml = 65.7 mg/l = $\frac{65.7}{40}$ mmoles/l = 1.643 mmoles/l.

Self-test 6.4

From the data given above calculate the concentration of mg in the haemodialysis solution in mmoles/l.

Answer: From computer fitting of the calibration line mg = 0.770 mmoles/l

Self-test 6.5

Zinc (Zn) is added to insulin to retard its rate of absorption into the bloodstream. The total concentration of Zn in Zn insulin suspension is determined by atomic absorption spectophotometry. From the following data calculate the total concentration of Zn in a Zn insulin suspension in percentage of w/v from the following data:

- Concentration of Zn in the standard solution used to prepare the calibration line = 50.5 mg/100 ml.
- Dilution 1: 5 ml of standard solution were diluted to 500 ml with 0.01 M HCl (diluted standard solution).
- The calibration line was prepared as follows: 10, 20, 30, 40 and 50 ml amounts of diluted standard solution were diluted to 100 ml with 0.01 M HCl.
- The following absorption readings were obtained: 0.151, 0.313, 0.454, 0.605 and 0.755. 2 ml of the Zn insulin suspension (100 units/ml) were diluted to 200 ml with 0.01 M HCl and the following reading was obtained: 0.595.

Answer: 0.01983% w/v

Some examples of limit tests employing AAS

Assay of lead in sugars

AAS is used in BP assays to conduct limit tests for lead and nickel in sugars and polyols. In this case, the concentrations of the metals are very low compared with the concentration of the sugar and thus it is not even possible to compensate for the interference by the sugar using the method of standard additions. In this case, the lead is extracted from a solution of the sugar by forming an organosoluble complex with ammonium pyrrolidinedithiocarbamate (APDC) and by then extracting the complex into organic solvent. The solution of the metal complex in the organic solvent is then assayed by AAS in comparison with a series of standards added to the sugar solution to form a calibration series based on the method of standard additions.

A limit test for lead in mannitol (the BP limit is set at 0.5 ppm) was carried out as follows:

(i) A solution containing 100 g of mannitol in 250 ml of water was prepared.
(ii) A standard solution containing 101.4 mg/100 ml of lead was prepared with 0.01 M HNO_3.
(iii) 10 ml of this solution was diluted to 1000 ml (diluted standard solution).
(iv) 4×50 ml aliquots of the mannitol solution were mixed, respectively, with: (a) 0, (b) 0.5 ml, (c) 1.0 ml and (d) 1.5 ml of diluted standard solution.
(v) Each sample was then mixed with a solution of APDC and the samples were then extracted with 10 ml 4-methylpentan-2-one. The organic layer was then separated and was then analysed by AAS.
(vi) The following readings were obtained: (a) 0.057, (b) 0.104 (c) 0.156 and (d) 0.217.

Calculate the lead content in the mannitol in ppm: ppm = μg/g of substance.

Calculation example 6.4

Diluted lead standard solution contains $\frac{101.4}{10} = 10.4$ mg/100 ml = 0.0104 mg/ml = 10.4 μg/ml.

101.4 g of mannitol were dissolved in 250 ml of solution, therefore in each 50 ml aliquot there was 20.28 g.

The amount of lead added to the four samples was: 0, $0.5 \times 10.4 = 5.2$ μg, $1 \times 10.4 = 10.4$ μg and $1.5 \times 10.4 = 15.6$ μg.

The equation for the line obtained by plotting amount of lead added against the readings is:
$y = 0.010\,x + 0.054$ ($r = 0.998$).

The negative intercept ($y = 0$) gives the content of lead in the sample.

$x = \frac{0.054}{0.01} = 5.4$ μg.

5.4 μg of lead is present in a solution containing 20.28 g of mannitol.

Lead content in the mannitol = $\frac{5.4}{20.28} = 0.266$ μg/g = 0.266 ppm.

Self-test 6.6

The procedure used to determine lead in mannitol was also used to determine nickel in a sample of mannitol. Calculate the content of nickel in a sample of mannitol from the following data:

- 100.5 g of mannitol was dissolved in 250 ml of water.
- A standard solution containing nickel at 10.6 ppm (10.6 μg/ml) was used to prepare a calibration series by adding 0.5 ml, 1.0 ml and 1.5 ml of the standard to 50 ml aliquots of the mannitol solution.
- The following readings were obtained: 0.378, 0.543, 0.718, 0.891. Calculate the content of nickel in ppm in the sample of mannitol.

Answer: 0.58 ppm

Trace metals in a silicone foam cavity wound dressing

This expandable wound dressing is prepared by mixing a silicone elastomer with an organotin catalyst to form an expandable dressing immediately prior to application. Most of the tin is not extractable from the dressing matrix but a limit test for extractable tin is carried out as follows:

(i) 5 g of dressing cut into pieces is shaken with 50 ml of 0.9% w/v sodium chloride for 4 h.

(ii) The solution is filtered and the tin is determined by AAS using a nitrous oxide/acetylene flame and measuring the absorption at 235.5 nm. The limit set for the tin is 6 ppm (6 μg/g).

(iii) The same solution is used to determine whether the sample passes 5 ppm limits for cadmium, copper, lead and zinc but using an air/acetylene flame and using the lamps appropriate for the detection of these elements.

Applications of AAS in BP assays

AAS is used in a number of limit tests for metallic impurities, e.g.: magnesium and strontium in calcium acetate; palladium in carbenicillin sodium and lead in bismuth subgallate. It is also used to assay metals in a number of other preparations: zinc in zinc insulin suspension and tetracosactrin zinc injection; copper and iron in ascorbic acid; zinc in acetylcysteine; lead in bismuthsubcarbonate; silver in cisplatinum; lead in oxyprenolol; aluminium in albumin solution and calcium, magnesium, mercury and zinc in water used for diluting haemodialysis solutions.

Inductively coupled plasma emission spectroscopy

If high enough temperatures can be reached, any element can be excited to a level where it will produce emission of radiation. Such high temperatures can be achieved by using plasma emission. A schematic diagram of an inductively coupled plasma (ICP) 'torch' is shown in Figure 6.6.

High temperatures are achieved by heating argon with high intensity radiofrequency radiation. At such high temperatures all elements will emit radiation as they are excited and then return to the ground state. In order to derive spectral information from the process an efficient monochromator and computer processing of the data are required in order to unscramble the large number of lines that are derived from a particular sample. ICP has been used to determine a complex of the metal ion dysprosium, which is used as a magnetic resonance imaging contrast agent, in serum.[1]

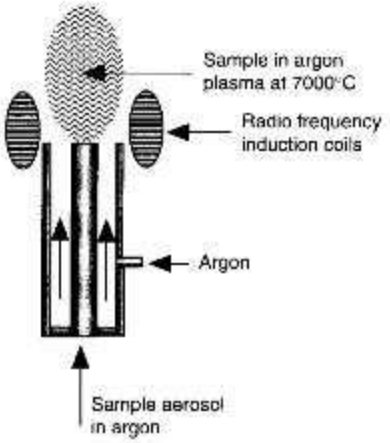

Fig. 6.6
Schematic diagram of an ICP torch.

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Further reading

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