Aluminium (*2.4.17*): maximum 0.2 ppm, if intended for use in the manufacture of dialysis solutions.

Prescribed solution. Dissolve 20 g in 100 ml of *water R* and adjust to pH 6.0 by the addition of *1 M hydrochloric acid* (about 10 ml).

Reference solution. Mix 2 ml of *aluminium standard solution (2 ppm Al) R*, 10 ml of *acetate buffer solution pH 6.0 R* and 98 ml of *water R*.

Blank solution. Mix 10 ml of *acetate buffer solution pH 6.0 R* and 100 ml of *water R*.

Arsenic (*2.4.2, Method A*): maximum 2 ppm, determined on 0.5 g.

Calcium and magnesium: maximum 50 ppm, calculated as Ca.

To 200 ml of *water R* add 10 ml of *ammonium chloride buffer solution pH 10.0 R*, 0.1 g of *mordant black 11 triturate R*, 2.0 ml of *0.05 M zinc chloride* and, dropwise, *0.02 M sodium edetate* until the colour changes from violet to blue. Add to the solution 10.0 g of the substance to be examined and shake to dissolve. Titrate with *0.02 M sodium edetate* until the blue colour is restored. Not more than 0.65 ml of *0.02 M sodium edetate* is required.

Heavy metals (*2.4.8*): maximum 10 ppm.

12 ml of solution S complies with test A. Prepare the reference solution using *lead standard solution (1 ppm Pb) R*.

Iron (*2.4.9*): maximum 10 ppm, determined on 10 ml of solution S.

Loss on drying (*2.2.32*): 39.0 per cent to 40.5 per cent, determined on 1.000 g by drying in an oven at 130 °C. Introduce the substance to be examined into the oven while the latter is cold.

ASSAY

Dissolve 0.250 g in 50 ml of *anhydrous acetic acid R*, add 5 ml of *acetic anhydride R*, mix and allow to stand for 30 min. Using 0.3 ml of *naphtholbenzein solution R* as indicator, titrate with *0.1 M perchloric acid* until a green colour is obtained.

1 ml of *0.1 M perchloric acid* is equivalent to 8.20 mg of $C_2H_3NaO_2$.

STORAGE

In an airtight container.

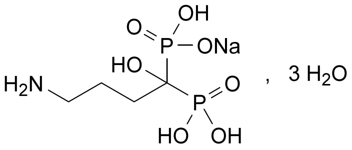
LABELLING

The label states, where applicable, that the substance is suitable for use in the manufacture of dialysis solutions.

01/2008:1564

SODIUM ALENDRONATE

Natrii alendronas



$C_4H_{12}NNaO_7P_2,3H_2O$ M_r 325.1
[121268-17-5]

DEFINITION

Sodium alendronate contains not less than 98.0 per cent and not more than the equivalent of 102.0 per cent of (4-amino-1-hydroxybutylidene)bisphosphonic acid monosodium salt, calculated with reference to the dried substance.

CHARACTERS

A white or almost white, crystalline powder, soluble in water, very slightly soluble in methanol, practically insoluble in methylene chloride.

IDENTIFICATION

A. Examine by infrared absorption spectrophotometry (*2.2.24*), comparing with the spectrum obtained with *sodium alendronate CRS*. Examine the substances prepared as discs.

B. It gives reaction (a) of sodium (*2.3.1*).

TESTS

Solution S. Dissolve 0.5 g in *carbon dioxide-free water R* prepared from *distilled water R* and dilute to 50 ml with the same solvent.

Appearance of solution. Solution S is clear (*2.2.1*) and not more intensely coloured than reference solution B_7 or BY_7 (*2.2.2, Method II*).

pH (*2.2.3*). The pH of is 4.0 to 5.0.

4-aminobutanoic acid. Examine by thin-layer chromatography (*2.2.27*), using a *TLC silica gel plate R*.

Test solution. Dissolve 0.10 g of the substance to be examined in *water R* and dilute to 10 ml with the same solvent.

Reference solution (a). Dissolve 0.10 g of *4-aminobutanoic acid R* in *water R* and dilute to 200 ml with the same solvent.

Reference solution (b). Dilute 1 ml of reference solution (a) to 10 ml with *water R*.

Apply to the plate 5 µl of the test solution and 5 µl of reference solution (b). Allow the plate to dry in air. Develop over a path of 15 cm using a mixture of 20 volumes of *water R*, 20 volumes of *glacial acetic acid R* and 60 volumes of *butanol R*. Dry the plate in a current of warm air. Spray with *ninhydrin solution R* and heat at 100 °C to 105 °C for 15 min. Any spots corresponding to 4-aminobutanoic acid in the chromatogram obtained with the test solution are not more intense than the spot in the chromatogram obtained with reference solution (b) (0.5 per cent).

Phosphate and phosphite. Examine the chromatograms obtained in the assay. In the chromatogram obtained with the test solution: the area of any peak corresponding to phosphate is not greater than that of the peak due to phosphate in the chromatogram obtained with reference solution (d) (0.5 per cent); the area of any peak corresponding to phosphite is not greater than that of the peak due to phosphite in the chromatogram obtained with reference solution (d) (0.5 per cent).

Heavy metals (*2.4.8*). 1.0 g complies with limit test F for heavy metals (20 ppm). Prepare the standard using 2 ml of *lead standard solution (10 ppm Pb) R*.

Loss on drying (*2.2.32*): 16.1 per cent to 17.1 per cent, determined on 1.000 g by drying in an oven at 140 °C to 145 °C.

ASSAY

Examine by liquid chromatography (*2.2.29*).

Test solution. Dissolve 50.0 mg of the substance to be examined in *water R* and dilute to 25.0 ml with the same solvent.

Reference solution (a). Dissolve 50.0 mg of *sodium alendronate CRS* in *water R* and dilute to 25.0 ml with the same solvent.

Reference solution (b). Dissolve 3.0 g of *phosphoric acid R* in *water R* and dilute to 100.0 ml with the same solvent. Dilute 1.0 ml of the solution to 100.0 ml with *water R.*

Reference solution (c). Dissolve 2.5 g of *phosphorous acid R* in *water R* and dilute to 100.0 ml with the same solvent. Dilute 1.0 ml of the solution to 100.0 ml with *water R.*

Reference solution (d). Mix 2.0 ml of reference solution (b) and 2.0 ml of reference solution (c) and dilute to 50.0 ml with *water R.*

The chromatographic procedure may be carried out using:

– a column 0.15 m long and 4.6 mm in internal diameter packed with *anion exchange resin R1* (7 µm),

– as mobile phase at a flow rate of 1.2 ml/min a solution of 0.2 ml of *anhydrous formic acid R* in 1000 ml of *water R,* adjusted to pH 3.5 with *2 M sodium hydroxide R,*

– as detector a refractometer,

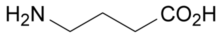
– a 100 µl loop injector,

maintaining the temperature of the column at 35 °C.

Inject reference solution (a) six times. The assay is not valid unless the relative standard deviation of the peak area of sodium alendronate is at most 1.0 per cent. Inject the test solution, reference solution (a) and reference solution (d). The retention time of sodium alendronate is about 16 min and the relative retention times are: phosphate about 1.3 and phosphite about 1.6. Record the chromatograms for twice the retention time of the principal peak in the chromatogram obtained with the test solution.

Calculate the percentage content of $C_4H_{12}NNaO_7P_2$ from the peak areas and the declared content of *sodium alendronate CRS.*

IMPURITIES



A. 4-aminobutanoic acid,

B. phosphate,

C. phosphite.

01/2008:0625
corrected 6.0

SODIUM ALGINATE

Natrii alginas

DEFINITION

Sodium alginate consists mainly of the sodium salt of alginic acid, which is a mixture of polyuronic acids $[C_6H_8O_6)_n]$ composed of residues of D-mannuronic acid and L-guluronic acid. Sodium alginate is obtained mainly from algae belonging to the Phaeophyceae.

CHARACTERS

Appearance: white or pale yellowish-brown powder.

Solubility: slowly soluble in water forming a viscous, colloidal solution, practically insoluble in ethanol (96 per cent).

IDENTIFICATION

A. Dissolve 0.2 g with shaking in 20 ml of *water R.* To 5 ml of this solution add 1 ml of *calcium chloride solution R.* A voluminous gelatinous mass is formed.

B. To 10 ml of the solution prepared in identification test A add 1 ml of *dilute sulphuric acid R.* A gelatinous mass is formed.

C. To 5 mg add 5 ml of *water R,* 1 ml of a freshly prepared 10 g/l solution of *1,3-dihydroxynaphthalene R* in *ethanol (96 per cent) R* and 5 ml of *hydrochloric acid R.* Boil for 3 min, cool, add 5 ml of *water R,* and shake with 15 ml of *di-isopropyl ether R.* Carry out a blank test. The upper layer obtained with the substance to be examined exhibits a deeper bluish-red colour than that obtained with the blank.

D. It complies with the test for sulphated ash. The residue obtained, dissolved in 2 ml of *water R,* gives reaction (a) of sodium (*2.3.1*).

TESTS

Solution S. Dissolve 0.10 g in *water R,* with constant stirring, dilute to 30 ml with the same solvent and allow to stand for 1 h.

Appearance of solution. The solution is not more opalescent than reference suspension II (*2.2.1*) and not more intensely coloured than intensity 6 of the range of reference solutions of the most appropriate colour (*2.2.2, Method II*).

Dilute 1 ml of solution S to 10 ml with *water R.*

Chlorides: maximum 1.0 per cent.

To 2.50 g add 50 ml of *dilute nitric acid R,* shake for 1 h and dilute to 100.0 ml with *dilute nitric acid R.* Filter. To 50.0 ml of the filtrate add 10.0 ml of *0.1 M silver nitrate* and 5 ml of *toluene R.* Titrate with *0.1 M ammonium thiocyanate,* using 2 ml of *ferric ammonium sulphate solution R2* as indicator and shaking vigorously towards the end point.

1 ml of *0.1 M silver nitrate* is equivalent to 3.545 mg of Cl.

Calcium: maximum 1.50 per cent.

Atomic absorption spectrometry (*2.2.23, Method II*).

Test solution. Dissolve 0.10 g in 50 ml of *dilute ammonia R2,* heating on a water-bath. Allow to cool and dilute to 100.0 ml with *distilled water R* (solution (a)). Dilute 3.0 ml of solution (a) to 100.0 ml with *distilled water R.*

Reference solutions. Prepare 3 reference solutions in the same manner as the test solution but add 0.75 ml, 1.0 ml and 1.5 ml respectively of *calcium standard solution (100 ppm Ca) R* to the 3.0 ml of solution (a).

Set the zero of the instrument using a mixture of 1.5 volumes of *dilute ammonia R2* and 98.5 volumes of *distilled water R.*

Source: calcium hollow-cathode lamp.

Wavelength: 422.7 nm.

Atomisation device: air-acetylene flame.

Heavy metals (*2.4.8*): maximum 20 ppm.

1.0 g complies with test F. Prepare the reference solution using 2 ml of *lead standard solution (10 ppm Pb) R.*

Loss on drying (*2.2.32*): maximum 15.0 per cent, determined on 0.1000 g by drying in an oven at 105 °C for 4 h.