buffer R and 3 mL of an 82 g/L solution of *anhydrous sodium acetate R*. Adjust to pH 5.2 with *ammonia R* and dilute to 50.0 mL with *distilled water R*.

Reference solutions. To 0.25 mL, 0.5 mL, 1.0 mL, 2.0 mL and 5.0 mL of *fluoride standard solution (10 ppm F) R* add 20.0 mL of *total-ionic-strength-adjustment buffer R* and dilute to 50.0 mL with *distilled water R*.

Indicator electrode: fluoride selective.

Reference electrode: silver-silver chloride.

Take into account the addition of fluoride to the test solution for the calculation.

Copper: maximum 5 ppm.

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

Test solution. Dissolve 2.0 g in a 9.7 g/L solution of *nitric acid R* and dilute to 25.0 mL with the same acid solution.

Reference solutions. Prepare the reference solutions using *copper standard solution (10 ppm Cu) R*, diluting with a 9.7 g/L solution of *nitric acid R*.

Source: copper hollow-cathode lamp.

Wavelength: 324.8 nm.

Atomisation device: air-acetylene flame.

Iron: maximum 2 ppm.

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

Test solution. Dissolve 5.0 g in a 9.7 g/L solution of *nitric acid R* and dilute to 25.0 mL with the same acid solution.

Reference solutions. Prepare the reference solutions using *iron standard solution (10 ppm Fe) R*, diluting with a 9.7 g/L solution of *nitric acid R*.

Source: iron hollow-cathode lamp.

Wavelength: 248.3 nm.

Atomisation device: air-acetylene flame.

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

2.0 g complies with test D. Prepare the reference solution using 2.0 mL of *lead standard solution (10 ppm Pb) R*.

Loss on drying (*2.2.32*): maximum 0.1 per cent, determined on 1.000 g by drying in an oven at 105 °C for 2 h.

ASSAY

Dissolve 80.0 mg in a mixture of 10 mL of *dilute sulfuric acid R* and 80 mL of *carbon dioxide-free water R*. Add 1 mL of *starch solution R*. Titrate with *0.05 M iodine* until a persistent violet-blue colour is obtained.

1 mL of *0.05 M iodine* is equivalent to 10.66 mg of $C_{12}H_{14}CaO_{12},2H_2O$.

STORAGE

In a non-metallic container, protected from light.

07/2008:0014

CALCIUM CARBONATE

Calcii carbonas

$CaCO_3$ M_r 100.1

[471-34-1]

DEFINITION

Content: 98.5 per cent to 100.5 per cent (dried substance).

CHARACTERS

Appearance: white or almost white powder.

Solubility: practically insoluble in water.

IDENTIFICATION

A. It gives the reaction of carbonates (*2.3.1*).

B. 0.2 mL of solution S (see Tests) gives the reactions of calcium (*2.3.1*).

TESTS

Solution S. Dissolve 5.0 g in 80 mL of *dilute acetic acid R*. When the effervescence ceases, boil for 2 min. Allow to cool, dilute to 100 mL with *dilute acetic acid R* and filter, if necessary, through a sintered-glass filter (*2.1.2*).

Substances insoluble in acetic acid: maximum 0.2 per cent.

Wash any residue obtained during the preparation of solution S with 4 quantities, each of 5 mL, of hot *water R* and dry at 100-105 °C for 1 h. The residue weighs a maximum of 10 mg.

Chlorides (*2.4.4*): maximum 330 ppm.

Dilute 3 mL of solution S to 15 mL with *water R*.

Sulfates (*2.4.13*): maximum 0.25 per cent.

Dilute 1.2 mL of solution S to 15 mL with *distilled water R*.

Arsenic (*2.4.2, Method A*): maximum 4 ppm, determined on 5 mL of solution S.

Barium. To 10 mL of solution S add 10 mL of *calcium sulfate solution R*. After at least 15 min, any opalescence in the solution is not more intense than that in a mixture of 10 mL of solution S and 10 mL of *distilled water R*.

Iron (*2.4.9*): maximum 200 ppm.

Dissolve 50 mg in 5 mL of *dilute hydrochloric acid R* and dilute to 10 mL with *water R*.

Magnesium and alkali metals: maximum 1.5 per cent.

Dissolve 1.0 g in 12 mL of *dilute hydrochloric acid R*. Boil the solution for about 2 min and add 20 mL of *water R*, 1 g of *ammonium chloride R* and 0.1 mL of *methyl red solution R*. Add *dilute ammonia R1* until the colour of the indicator changes and then add 2 mL in excess. Heat to boiling and add 50 mL of hot *ammonium oxalate solution R*. Allow to stand for 4 h, dilute to 100 mL with *water R* and filter through a suitable filter. To 50 mL of the filtrate add 0.25 mL of *sulfuric acid R*. Evaporate to dryness on a water-bath and ignite to constant mass at 600 ± 50 °C. The residue weighs a maximum of 7.5 mg.

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

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

Loss on drying (*2.2.32*): maximum 2.0 per cent, determined on 1.000 g by drying in an oven at 200 ± 10 °C.

ASSAY

Dissolve 0.150 g in a mixture of 3 mL of *dilute hydrochloric acid R* and 20 mL of *water R*. Boil for 2 min, allow to cool and dilute to 50 mL with *water R*. Carry out the complexometric titration of calcium (*2.5.11*).

1 mL of *0.1 M sodium edetate* is equivalent to 10.01 mg of $CaCO_3$.

FUNCTIONALITY-RELATED CHARACTERISTICS

This section provides information on characteristics that are recognised as being relevant control parameters for one or more functions of the substance when used as an excipient (see chapter 5.15). This section is a non-mandatory part of the monograph and it is not necessary to verify the characteristics to demonstrate compliance. Control of these characteristics can however contribute to the quality of a medicinal product by improving the consistency of the manufacturing process and the performance of the medicinal product during use. Where control methods are cited, they are recognised as being suitable for the purpose, but other methods can also be used. Wherever results for a particular characteristic are reported, the control method must be indicated.

The following characteristics may be relevant for calcium carbonate used as filler in tablets and capsules.

Particle-size distribution (*2.9.31* or *2.9.38*).

Powder flow (*2.9.36*).

01/2008:0015
corrected 6.0

CALCIUM CHLORIDE DIHYDRATE

Calcii chloridum dihydricum

$CaCl_2,2H_2O$ M_r 147.0
[10035-04-8]

DEFINITION

Content: 97.0 per cent to 103.0 per cent of $CaCl_2,2H_2O$.

CHARACTERS

Appearance: white or almost white, crystalline powder, hygroscopic.

Solubility: freely soluble in water, soluble in ethanol (96 per cent).

IDENTIFICATION

A. Solution S (see Tests) gives reaction (a) of chlorides (*2.3.1*).

B. It gives the reactions of calcium (*2.3.1*).

C. It complies with the limits of the assay.

TESTS

Solution S. Dissolve 10.0 g in *carbon dioxide-free water R* prepared from *distilled water R* and dilute to 100 mL with the same solvent.

Appearance of solution. Solution S is clear (*2.2.1*) and not more intensely coloured than reference solution Y_6 (*2.2.2, Method II*).

Acidity or alkalinity. To 10 mL of freshly prepared solution S add 0.1 mL of *phenolphthalein solution R*. If the solution is red, not more than 0.2 mL of *0.01 M hydrochloric acid* is required to discharge the colour and if the solution is colourless, not more than 0.2 mL of *0.01 M sodium hydroxide* is required to turn it red.

Sulfates (*2.4.13*): maximum 300 ppm.

Dilute 5 mL of solution S to 15 mL with *distilled water R*.

Aluminium. To 10 mL of solution S add 2 mL of *ammonium chloride solution R* and 1 mL of *dilute ammonia R1* and boil the solution. No turbidity or precipitate is formed.

If intended for use in the manufacture of dialysis solutions, the above test is replaced by the following test for aluminium (*2.4.17*): maximum 1 ppm.

Prescribed solution. Dissolve 4 g in 100 mL of *water R* and add 10 mL of *acetate buffer solution pH 6.0 R*.

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*.

Barium. To 10 mL of solution S add 1 mL of *calcium sulfate solution R*. After at least 15 min, any opalescence in the solution is not more intense than that in a mixture of 1 mL of *distilled water R* and 10 mL of solution S.

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

Magnesium and alkali metals: maximum 0.5 per cent.

To a mixture of 20 mL of solution S and 80 mL of *water R* add 2 g of *ammonium chloride R* and 2 mL of *dilute ammonia R1*, heat to boiling and pour into the boiling solution a hot solution of 5 g of *ammonium oxalate R* in 75 mL of *water R*. Allow to stand for 4 h, dilute to 200 mL with *water R* and filter through a suitable filter. To 100 mL of the filtrate add 0.5 mL of *sulfuric acid R*. Evaporate to dryness on a water-bath and ignite to constant mass at 600 ± 50 °C. The residue weighs a maximum of 5 mg.

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

12 mL of solution S complies with test A. Prepare the reference solution using *lead standard solution (2 ppm Pb) R*.

ASSAY

Dissolve 0.280 g in 100 mL of *water R* and carry out the complexometric titration of calcium (*2.5.11*).

1 mL of *0.1 M sodium edetate* is equivalent to 14.70 mg of $CaCl_2,2H_2O$.

LABELLING

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

STORAGE

In an airtight container.

01/2008:0707
corrected 6.0

CALCIUM CHLORIDE HEXAHYDRATE

Calcii chloridum hexahydricum

$CaCl_2,6H_2O$ M_r 219.1
[7774-34-7]

DEFINITION

Content: 97.0 per cent to 103.0 per cent of $CaCl_2,6H_2O$.

CHARACTERS

Appearance: white or almost white, crystalline mass or colourless crystals.

Solubility: very soluble in water, freely soluble in ethanol (96 per cent).

It solidifies at about 29 °C.

IDENTIFICATION

A. Solution S (see Tests) gives reaction (a) of chlorides (*2.3.1*).

B. It gives the reactions of calcium (*2.3.1*).

C. It complies with the limits of the assay.

TESTS

Solution S. Dissolve 15.0 g in *carbon dioxide-free water R* prepared from *distilled water R* and dilute to 100 mL with the same solvent.

Appearance of solution. Solution S is clear (*2.2.1*) and not more intensely coloured than reference solution Y_6 (*2.2.2, Method II*).

Acidity or alkalinity. To 10 mL of freshly prepared solution S add 0.1 mL of *phenolphthalein solution R*. If the solution is red, not more than 0.2 mL of *0.01 M hydrochloric acid* is required to discharge the colour and if the solution is colourless, not more than 0.2 mL of *0.01 M sodium hydroxide* is required to turn it red.

Sulfates (*2.4.13*): maximum 200 ppm.

Dilute 5 mL of solution S to 15 mL with *distilled water R*.

Aluminium. To 10 mL of solution S add 2 mL of *ammonium chloride solution R* and 1 mL of *dilute ammonia R1*. Heat to boiling. No turbidity or precipitate is formed.

If intended for use in the manufacture of dialysis solutions, the above test is replaced by the following test for aluminium (*2.4.17*): maximum 1 ppm.

Prescribed solution. Dissolve 6 g in 100 mL of *water R* and add 10 mL of *acetate buffer solution pH 6.0 R*.

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*.