Column:

– *size*: *l* = 0.25 m, Ø = 4.6 mm,

– *stationary phase*: *octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase: dissolve 1.56 g of *sodium dihydrogen phosphate R* in 1000 ml of *water R* and adjust to pH 2.5 with a 10 per cent *V/V* solution of *phosphoric acid R*.

Flow rate: 1.5 ml/min.

Detection: spectrophotometer at 210 nm.

Injection: 10 µl loop injector; inject the test solution and reference solutions (b), (c), (d) and (e).

Run time: 4 times the retention time of pidolic acid.

Retention times: pidolic acid = about 4.5 min; impurity B = about 7.5 min.

System suitability: reference solution (e):

– *resolution*: minimum 10 between the peaks due to pidolic acid and to impurity B.

Limits:

– *impurity B*: not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (1.0 per cent),

– *total of other impurities*: not more than half of the area of the principal peak in the chromatogram obtained with reference solution (b) (0.5 per cent),

– *disregard limit*: not more than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (c) (0.05 per cent); disregard any peak corresponding to the nitrate ion (NO_3^-).

Impurity A. Thin-layer chromatography (*2.2.27*).

Test solution. Dissolve 0.250 g of the substance to be examined in 4 ml of *water R* and dilute to 50.0 ml with *methanol R*.

Reference solution (a). Dissolve 60.0 mg of *glutamic acid R* in 50 ml of *water R* and dilute to 100.0 ml with *methanol R*. Dilute 1.0 ml of the solution to 20.0 ml with *methanol R*.

Reference solution (b). Dissolve 10 mg of *glutamic acid R* and 10 mg of *aspartic acid R* in *water R* and dilute to 25 ml with the same solvent. Dilute 1 ml of the solution to 10 ml with *water R*.

Plate: *TLC silica gel plate R*.

Mobile phase: *glacial acetic acid R, water R, butanol R* (20:20:60 *V/V/V*).

Application: 5 µl.

Development: over 2/3 of the plate.

Drying: in air.

Detection: spray with *ninhydrin solution R* and heat at 100-105 °C for 15 min.

System suitability: the test is not valid unless the chromatogram obtained with reference solution (b) shows 2 clearly separated spots.

Limit:

– *impurity A*: any spot corresponding to impurity A in the chromatogram obtained with the test solution is not more intense that the spot in the chromatogram obtained with reference solution (a) (0.6 per cent).

Chlorides (*2.4.4*): maximum 500 ppm.

Dilute 1.0 ml of solution S to 15.0 ml of *water R*. The solution complies with the limit test for chlorides.

Nitrates. Examine the chromatogram obtained with the test solution in the test for related substances.

Limit:

– *nitrates*: not more than the area of the principal peak in the chromatogram obtained with reference solution (d) (200 ppm).

Sulphates (*2.4.13*): maximum 0.1 per cent.

Dilute 1.5 ml of solution S to 15.0 ml with *distilled water R*. The solution complies with the limit test for sulphates.

Arsenic (*2.4.2*): maximum 2 ppm.

5.0 ml of solution S complies with limit test A.

Iron (*2.4.9*): maximum 200 ppm.

Dilute 0.5 ml of solution S to 10 ml of *water R*. The solution complies with the limit test for iron.

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

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

Water (*2.5.12*): maximum 8.0 per cent, determined on 0.200 g.

ASSAY

Dissolve 0.300 g in 50 ml of *water R*. Carry out the complexometric titration of magnesium (*2.5.11*).

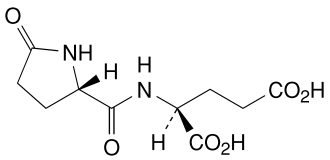
1 ml of *0.1 M sodium edetate* is equivalent to 2.431 mg of Mg.

STORAGE

In an airtight container.

IMPURITIES

A. glutamic acid,



B. (2*S*)-2-[[[(2*S*)-5-oxopyrrolidin-2-yl]carbonyl]amino]pentanedioic acid.

01/2008:0229
corrected 6.0

MAGNESIUM STEARATE

Magnesii stearas

DEFINITION

Magnesium stearate is a mixture of magnesium salts of different fatty acids consisting mainly of stearic (octadecanoic) acid [$(C_{17}H_{35}COO)_2Mg$; M_r 591.3] and palmitic (hexadecanoic) acid [$(C_{15}H_{31}COO)_2$ Mg; M_r 535.1] with minor proportions of other fatty acids. It contains not less than 4.0 per cent and not more than 5.0 per cent of Mg (A_r 24.30), calculated with reference to the dried substance. The fatty acid fraction contains not less than 40.0 per cent of stearic acid and the sum of stearic acid and palmitic acid is not less than 90.0 per cent.

CHARACTERS

A white or almost white, very fine, light powder, greasy to the touch, practically insoluble in water and in ethanol.

IDENTIFICATION

First identification: C, D.

Second identification: A, B, D.

A. The residue obtained in the preparation of solution S (see Tests) has a freezing point (*2.2.18*) not lower than 53 °C.

B. The acid value of the fatty acids (*2.5.1*) is 195 to 210, determined on 0.200 g of the residue obtained in the preparation of solution S dissolved in 25 ml of the prescribed mixture of solvents.

C. Examine the chromatograms obtained in the test for fatty acid composition. The retention times of the principal peaks in the chromatogram obtained with the test solution are approximately the same as those of the principal peaks in the chromatogram obtained with the reference solution.

D. 1 ml of solution S gives the reaction of magnesium (*2.3.1*).

TESTS

Solution S. To 5.0 g add 50 ml of *peroxide-free ether R*, 20 ml of *dilute nitric acid R* and 20 ml of *distilled water R* and heat under a reflux condenser until dissolution is complete. Allow to cool. In a separating funnel, separate the aqueous layer and shake the ether layer with 2 quantities, each of 4 ml, of *distilled water R*. Combine the aqueous layers, wash with 15 ml of *peroxide-free ether R* and dilute to 50 ml with *distilled water R* (solution S). Evaporate the organic layer to dryness and dry the residue at 100-105 °C. Keep the residue for identification tests A and B.

Acidity or alkalinity. To 1.0 g add 20 ml of *carbon dioxide-free water R* and boil for 1 min with continuous stirring. Cool and filter. To 10 ml of the filtrate add 0.05 ml of *bromothymol blue solution R1*. Not more than 0.5 ml of *0.01 M hydrochloric acid* or *0.01 M sodium hydroxide* is required to change the colour of the indicator.

Chlorides (*2.4.4*). 0.5 ml of solution S diluted to 15 ml with *water R* complies with the limit test for chlorides (0.1 per cent).

Sulphates (*2.4.13*). 0.3 ml of solution S diluted to 15 ml with *distilled water R* complies with the limit test for sulphates (0.5 per cent).

Cadmium. Not more than 3.0 ppm of Cd, determined by atomic absorption spectrometry (*2.2.23, Method II*).

Test solution. Place 50.0 mg of the substance to be examined in a polytetrafluoroethylene digestion bomb and add 0.5 ml of a mixture of 1 volume of *hydrochloric acid R* and 5 volumes of *cadmium- and lead-free nitric acid R*. Allow to digest at 170 °C for 5 h. Allow to cool. Dissolve the residue in *water R* and dilute to 5.0 ml with the same solvent.

Reference solutions. Prepare the reference solutions using *cadmium standard solution (10 ppm Cd) R*, diluted as necessary with a 1 per cent *V/V* solution of *hydrochloric acid R*.

Measure the absorbance at 228.8 nm, using a cadmium hollow-cathode lamp as a source of radiation and a graphite furnace as atomic generator.

Lead. Not more than 10.0 ppm of Pb, determined by atomic absorption spectrometry (*2.2.23, Method II*).

Test solution. Use the solution described in the test for cadmium.

Reference solutions. Prepare the reference solutions using *lead standard solution (10 ppm Pb) R*, diluted as necessary with *water R*.

Measure the absorbance at 283.3 nm, using a lead hollow-cathode lamp as a source of radiation and a graphite furnace as atomic generator, depending on the apparatus the line at 217.0 nm may be used.

Nickel. Not more than 5.0 ppm of Ni, determined by atomic absorption spectrometry (*2.2.23, Method II*).

Test solution. Use the solution described in the test for cadmium.

Reference solutions. Prepare the reference solutions using *nickel standard solution (10 ppm Ni) R*, diluted as necessary with *water R*.

Measure the absorbance at 232.0 nm, using a nickel hollow-cathode lamp as a source of radiation and a graphite furnace as atomic generator.

Loss on drying (*2.2.32*). Not more than 6.0 per cent, determined on 1.000 g by drying in an oven at 105 °C.

Microbial contamination. Total viable aerobic count (*2.6.12*) not more than 10^3 micro-organisms per gram, determined by plate count. It complies with the test for *Escherichia coli* (*2.6.13*).

ASSAY

Magnesium. To 0.500 g in a 250 ml conical flask add 50 ml of a mixture of equal volumes of *butanol R* and *ethanol R*, 5 ml of *concentrated ammonia R*, 3 ml of *ammonium chloride buffer solution pH 10.0 R*, 30.0 ml of *0.1 M sodium edetate* and 15 mg of *mordant black 11 triturate R*. Heat to 45-50 °C until the solution is clear and titrate with *0.1 M zinc sulphate* until the colour changes from blue to violet. Carry out a blank titration.

1 ml of *0.1 M sodium edetate* is equivalent to 2.431 mg of Mg.

Fatty acid composition. Examine by gas chromatography (*2.2.28*).

Test solution. In a conical flask fitted with a reflux condenser, dissolve 0.10 g of the substance to be examined in 5 ml of *boron trifluoride-methanol solution R*. Boil under a reflux condenser for 10 min. Add 4 ml of *heptane R* through the condenser and boil again under a reflux condenser for 10 min. Allow to cool. Add 20 ml of a *saturated sodium chloride solution R*. Shake and allow the layers to separate. Remove about 2 ml of the organic layer and dry over 0.2 g of *anhydrous sodium sulphate R*. Dilute 1.0 ml of the solution to 10.0 ml with *heptane R*.

Reference solution. Prepare the reference solution in the same manner as the test solution using 50.0 mg of *palmitic acid CRS* and 50.0 mg of *stearic acid CRS* instead of magnesium stearate.

The chromatographic procedure may be carried out using:

– a fused-silica column 30 m long and 0.32 mm in internal diameter coated with *macrogol 20 000 R* (film thickness 0.5 µm),

– *helium for chromatography R* as the carrier gas at a flow rate of 2.4 ml/min,

– a flame-ionisation detector,

with the following temperature programme:

	Time (min)	Temperature (°C)	Rate (°C/min)	Comment
Column	0 - 2	70	–	isothermal
	2 - 36	70 → 240	5	linear gradient
	36 - 41	240	–	isothermal
Injection port		220		
Detector		260		

Inject 1 µl of the reference solution. When the chromatogram is recorded in the prescribed conditions, the relative retention of methyl palmitate to that of methyl stearate is about 0.88. The test is not valid unless, in the chromatogram obtained

with the reference solution, the resolution between the peaks corresponding to methyl stearate and methyl palmitate is at least 5.0.

Inject 1 µl of the test solution. Calculate the percentage content of stearic acid and palmitic acid from the areas of the peaks in the chromatogram obtained with the test solution by the normalisation procedure, disregarding the peak due to the solvent.

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. 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 characteristic may be relevant for magnesium stearate used as a lubricant in solid dosage forms (compressed and powder).

Specific surface area (*2.9.26, Method I*). Determine the specific surface area in the P/P_0 range of 0.05 to 0.15.

Sample outgassing: 2 h at 40 °C.

01/2008:0044
corrected 6.0

MAGNESIUM SULPHATE HEPTAHYDRATE

Magnesii sulfas heptahydricus

$MgSO_4,7H_2O$ M_r 246.5
[10034-99-8]

DEFINITION

Content: 99.0 per cent to 100.5 per cent (dried substance).

CHARACTERS

Appearance: white or almost white, crystalline powder or brilliant, colourless crystals.

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

IDENTIFICATION

A. It gives the reactions of sulphates (*2.3.1*).

B. It gives the reaction of magnesium (*2.3.1*).

TESTS

Solution S. Dissolve 5.0 g in *water R* and dilute to 50 ml with the same solvent.

Appearance of solution. Solution S is clear (*2.2.1*) and colourless (*2.2.2, Method II*).

Acidity or alkalinity. To 10 ml of solution S add 0.05 ml of *phenol red solution R*. Not more than 0.2 ml of *0.01 M hydrochloric acid* or *0.01 M sodium hydroxide* is required to change the colour of the indicator.

Chlorides (*2.4.4*): maximum 300 ppm.

Dilute 1.7 ml of solution S to 15 ml with *water R*.

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

Iron (*2.4.9*): maximum 20 ppm.

Dilute 5 ml of solution S to 10 ml with *water R*.

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*.

Loss on drying (*2.2.32*): 48.0 per cent to 52.0 per cent, determined on 0.500 g by drying in an oven at 110-120 °C for 1 h and then at 400 °C to constant mass.

ASSAY

Dissolve 0.450 g in 100 ml of *water R* and carry out the complexometric titration of magnesium (*2.5.11*).

1 ml of *0.1 M sodium edetate* is equivalent to 12.04 mg of $MgSO_4$.

01/2008:0403
corrected 6.0

MAGNESIUM TRISILICATE

Magnesii trisilicas

DEFINITION

It has a variable composition corresponding approximately to $Mg_2Si_3O_8,xH_2O$.

Content:

– *magnesium oxide* (MgO; M_r 40.30): minimum 29.0 per cent (ignited substance),

– *silicon dioxide* (SiO_2; M_r 60.1): minimum 65.0 per cent (ignited substance).

CHARACTERS

Appearance: white or almost white powder.

Solubility: practically insoluble in water and in ethanol (96 per cent).

IDENTIFICATION

A. 0.25 g gives the reaction of silicates (*2.3.1*).

B. 1 ml of solution S (see Tests) neutralised with *dilute sodium hydroxide solution R* gives the reaction of magnesium (*2.3.1*).

TESTS

Solution S. To 2.0 g add a mixture of 4 ml of *nitric acid R* and 4 ml of *distilled water R*. Heat to boiling with frequent shaking. Add 12 ml of *distilled water R* and allow to cool. Filter or centrifuge to obtain a clear solution and dilute to 20 ml with *distilled water R*.

Alkalinity. To 10.0 g in a 200 ml conical flask, add 100.0 g of *water R* and heat on a water-bath for 30 min. Allow to cool and make up to the initial mass with *water R*. Allow to stand and filter or centrifuge until a clear liquid is obtained. To 10 ml of this liquid add 0.1 ml of *phenolphthalein solution R*. Not more than 1.0 ml of *0.1 M hydrochloric acid* is required to change the colour of the indicator.

Water-soluble salts: maximum 1.5 per cent.

In a platinum dish, evaporate to dryness on a water-bath 20.0 ml of the liquid obtained in the test for alkalinity. The residue, ignited to constant mass at 900 ± 50 °C, weighs a maximum of 30 mg.