Acidity. To 10 mL of solution S add 1 mL of *phenolphthalein solution R*. Not more than 0.4 mL of *0.1 M sodium hydroxide* is required to change the colour of the indicator to red.

Methanol. Gas chromatography (*2.2.28*).

Internal standard solution. Dilute 10 mL of *ethanol R1* to 100 mL with *water R*.

Test solution. To 10.0 mL of the solution to be examined add 10.0 mL of the internal standard solution and dilute to 100.0 mL with *water R*.

Reference solution. To 1.0 mL of *methanol R* add 10.0 mL of the internal standard solution and dilute to 100.0 mL with *water R*.

Column:

- *material*: glass,
- *size*: *l* = 1.5-2.0 m, Ø = 2-4 mm,
- *stationary phase*: *ethylvinylbenzene-divinylbenzene copolymer R* (150-180 µm).

Carrier gas: *nitrogen for chromatography R*.

Flow rate: 30-40 mL/min.

Temperature:

- *column*: 120 °C,
- *injection port and detector*: 150 °C.

Detection: flame ionisation.

Injection: 1 µL of the test solution and the reference solution.

System suitability: reference solution:

- *resolution*: minimum 2.0 between the peaks due to methanol and ethanol.

Limit:

- *methanol*: 9.0 per cent *V/V* to 15.0 per cent *V/V*.

Sulfated ash (*2.4.14*): maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Into a 100 mL volumetric flask containing 2.5 mL of *water R* and 1 mL of *dilute sodium hydroxide solution R*, introduce 1.000 g of the solution to be examined, shake and dilute to 100.0 mL with *water R*. To 10.0 mL of the solution add 30.0 mL of *0.05 M iodine*. Mix and add 10 mL of *dilute sodium hydroxide solution R*. After 15 min, add 25 mL of *dilute sulfuric acid R* and 2 mL of *starch solution R*. Titrate with *0.1 M sodium thiosulfate*.

1 mL of *0.05 M iodine* is equivalent to 1.501 mg of CH_2O.

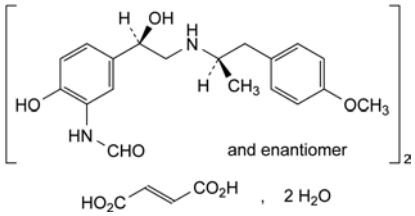
STORAGE

Protected from light, at a temperature of 15 °C to 25 °C.

01/2008:1724
corrected 7.0

FORMOTEROL FUMARATE DIHYDRATE

Formoteroli fumaras dihydricus



$C_{42}H_{52}N_4O_{12},2H_2O$ M_r 841

DEFINITION

N-[2-Hydroxy-5-[(1*RS*)-1-hydroxy-2-[[(1*RS*)-2-(4-methoxyphenyl)-1-methylethyl]amino]ethyl]phenyl]formamide (*E*)-butenedioate dihydrate.

Content: 98.5 per cent to 101.5 per cent (anhydrous substance).

CHARACTERS

Appearance: white or almost white or slightly yellow powder.

Solubility: slightly soluble in water, soluble in methanol, slightly soluble in 2-propanol, practically insoluble in acetonitrile.

IDENTIFICATION

Infrared absorption spectrophotometry (*2.2.24*).

Comparison: *formoterol fumarate dihydrate CRS*.

TESTS

pH (*2.2.3*): 5.5 to 6.5.

Dissolve 20 mg in *carbon dioxide-free water R* while heating to about 40 °C, allow to cool and dilute to 20 mL with the same solvent.

Optical rotation (*2.2.7*): – 0.10° to + 0.10°.

Dissolve 0.25 g in *methanol R* and dilute to 25.0 mL with the same solvent.

Related substances. Liquid chromatography (*2.2.29*).

Solution A. Dissolve 6.10 g of *sodium dihydrogen phosphate monohydrate R* and 1.03 g of *disodium hydrogen phosphate dihydrate R* in *water R* and dilute to 1000 mL with the same solvent. The pH is 6.0 ± 0.1.

Solvent mixture: *acetonitrile R*, solution A (16:84 *V/V*).

Test solution. Dissolve 20.0 mg of the substance to be examined in the solvent mixture and dilute to 100.0 mL with the solvent mixture. *Inject within 4 h of preparation, or within 24 h if stored protected from light at 4 °C.*

Reference solution (a). Dissolve 5 mg of *formoterol fumarate for system suitability CRS* (containing impurities A, B, C, D, E, F and G) in the solvent mixture and dilute to 25.0 mL with the solvent mixture.

Reference solution (b). Dilute 1.0 mL of the test solution to 25.0 mL with the solvent mixture. Dilute 1.0 mL of this solution to 20.0 mL with the solvent mixture.

Column:

- *size*: *l* = 0.15 m, Ø = 4.6 mm;
- *stationary phase*: spherical *octylsilyl silica gel for chromatography R3* (5 µm) with a pore size of 8 nm.

Mobile phase:

- *mobile phase A*: *acetonitrile R1*;
- *mobile phase B*: dissolve 3.73 g of *sodium dihydrogen phosphate monohydrate R* and 0.35 g of *phosphoric acid R* in *water R* and dilute to 1000 mL with the same solvent; the pH is 3.1 ± 0.1;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 10	16	84
10 - 37	16 → 70	84 → 30

Flow rate: 1.0 mL/min.

Detection: spectrophotometer at 214 nm.

Injection: 20 µL; inject the solvent mixture until a repeatable profile is obtained.

Identification of impurities: use the chromatogram obtained with reference solution (a) and the chromatogram supplied with *formoterol for system suitability CRS* to identify the peaks.

Relative retention with reference to formoterol (retention time = about 12 min): impurity G = about 0.4; impurity A = about 0.5; impurity B = about 0.7; impurity C = about 1.2; impurity D = about 1.3; impurity E = about 1.8; impurity F = about 2.0; impurity H = about 2.2.

System suitability: reference solution (a):

- *resolution*: minimum 1.5 between the peaks due to impurity G and impurity A.

– *peak-to-valley ratio*: minimum 2.5, where H_p = height above the baseline of the peak due to impurity C and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to formoterol.

Limits:

– *correction factor*: for the calculation of content, multiply the peak area of impurity A by 1.75;
– *impurity A*: not more than 1.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.3 per cent);
– *impurities B, C, D, F*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.2 per cent);
– *impurity E*: not more than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.1 per cent);
– *unspecified impurities*: for each impurity, not more than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.10 per cent);
– *total*: not more than 2.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.5 per cent);
– *disregard limit*: 0.25 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent).

Impurity I. Liquid chromatography (*2.2.29*).

Test solution. Dissolve 5.0 mg of the substance to be examined in *water R* and dilute to 50.0 mL with the same solvent. Sonicate if necessary.

Reference solution (a). Dissolve 5.0 mg of *formoterol for impurity I identification CRS* in *water R* and dilute to 50.0 mL with the same solvent. Sonicate if necessary.

Reference solution (b). Dilute 1.0 mL of the test solution to 20.0 mL with *water R*. Dilute 1.0 mL of this solution to 25.0 mL with *water R*.

Column:

– *size*: *l* = 0.15 m, Ø = 4.6 mm;
– *stationary phase*: *octadecyl vinyl polymer for chromatography R*.

Mobile phase: mix 12 volumes of *acetonitrile R1* with 88 volumes of a 5.3 g/L solution of *tripotassium phosphate trihydrate R* previously adjusted to pH 12.0 ± 0.1 with a 280 g/L solution of *potassium hydroxide R* or *phosphoric acid R*.

Flow rate: 0.5 mL/min.

Detection: spectrophotometer at 225 nm.

Injection: 20 µL.

Elution order: formoterol, impurity I.

System suitability: reference solution (a):

– *peak-to-valley ratio*: minimum 2.5, where H_p = height above the baseline of the peak due to impurity I and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to formoterol.

Limit:

– *impurity I*: not more than 1.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.3 per cent).

Water (*2.5.12*): 4.0 per cent to 5.0 per cent, determined on 0.100 g.

ASSAY

Dissolve 0.350 g in 50 mL of *anhydrous acetic acid R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (*2.2.20*).

1 mL of *0.1 M perchloric acid* is equivalent to 40.24 mg of $C_{42}H_{52}N_4O_{12}$.

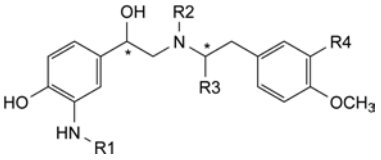
STORAGE

Protected from light.

IMPURITIES

Specified impurities: A, B, C, D, E, F, I.

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph *Substances for pharmaceutical use (2034)*. It is therefore not necessary to identify these impurities for demonstration of compliance. See also *5.10. Control of impurities in substances for pharmaceutical use*): *G, H.*



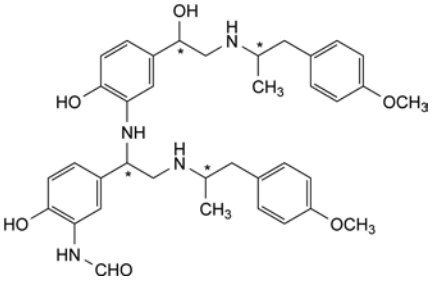
A. R1 = R2 = R4 = H, R3 = CH_3: 1-(3-amino-4-hydroxyphenyl)-2-[[2-(4-methoxyphenyl)-1-methylethyl]amino]ethanol,

B. R1 = CHO, R2 = R3 = R4 = H: *N*-[2-hydroxy-5-[(1*RS*)-1-hydroxy-2-[[2-(4-methoxyphenyl)ethyl]amino]ethyl]phenyl]formamide,

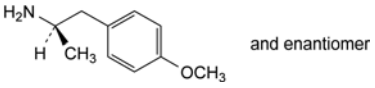
C. R1 = CO-CH_3, R2 = R4 = H, R3 = CH_3: *N*-[2-hydroxy-5-[1-hydroxy-2-[[2-(4-methoxyphenyl)-1-methylethyl]amino]ethyl]phenyl]acetamide,

D. R1 = CHO, R2 = R3 = CH_3, R4 = H: *N*-[2-hydroxy-5-[1-hydroxy-2-[methyl[2-(4-methoxyphenyl)-1-methylethyl]amino]ethyl]phenyl]formamide,

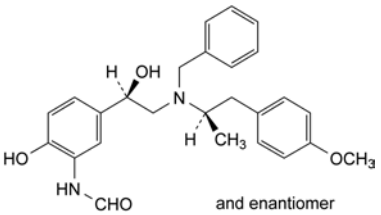
E. R1 = CHO, R2 = H, R3 = R4 = CH_3: *N*-[2-hydroxy-5-[1-hydroxy-2-[[2-(4-methoxy-3-methylphenyl)-1-methylethyl]amino]ethyl]phenyl]formamide,



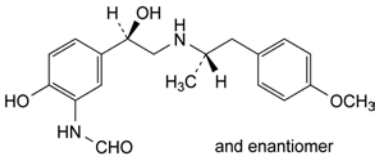
F. *N*-[2-hydroxy-5-[1-[[2-hydroxy-5-[1-hydroxy-2-[[2-(4-methoxyphenyl)-1-methylethyl]amino]ethyl]phenyl]amino]-2-[[2-(4-methoxyphenyl)-1-methylethyl]amino]ethyl]phenyl]formamide,



G. (2*RS*)-1-(4-methoxyphenyl)propan-2-amine,



H. *N*-[5-[(1*RS*)-2-[benzyl[(1*RS*)-2-(4-methoxyphenyl)-1-methylethyl]amino]-1-hydroxyethyl]-2-hydroxyphenyl]formamide (monobenzyl analogue),

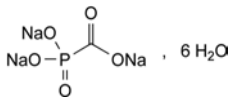


I. *N*-[2-hydroxy-5-[(1*RS*)-1-hydroxy-2-[[(1*SR*)-2-(4-methoxyphenyl)-1-methylethyl]amino]ethyl]phenyl]formamide (diastereoisomer).

07/2010:1520

FOSCARNET SODIUM HEXAHYDRATE

Foscarnetum natricum hexahydricum



$CNa_3O_5P,6H_2O$ M_r 300.0
[34156-56-4]

DEFINITION

Trisodium phosphonatoformate hexahydrate.

Content: 98.5 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance: white or almost white, crystalline powder.

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

IDENTIFICATION

A. Infrared absorption spectrophotometry (*2.2.24*).
Comparison: *foscarnet sodium hexahydrate CRS*.

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

TESTS

Solution S. Dissolve 0.5 g in *carbon dioxide-free water R* and dilute to 25 mL with the same solvent.

Appearance of solution. Solution S is not more opalescent than reference suspension I (*2.2.1*) and is colourless (*2.2.2, Method II*).

pH (*2.2.3*): 9.0 to 11.0 for solution S.

Impurity D. Gas chromatography (*2.2.28*).

Test solution. Dissolve 0.250 g of the substance to be examined in 9.0 mL of *0.1 M acetic acid* using a magnetic stirrer. Add 1.0 mL of *anhydrous ethanol R* and mix.

Reference solution. Dissolve 25.0 mg of *foscarnet impurity D CRS* in *anhydrous ethanol R* and dilute to 100.0 mL with the same solvent. Dilute 1.0 mL of this solution to 10.0 mL with *anhydrous ethanol R*.

Column:
- *material*: fused silica;
- *size*: *l* = 25 m, Ø = 0.31 mm;
- *stationary phase*: *poly(dimethyl)(diphenyl)(divinyl)-siloxane R* (film thickness 0.5 µm).

Carrier gas: *helium for chromatography R*.

Split ratio: 1:20.

Temperature:

	Time (min)	Temperature (°C)
Column	0 - 8	100 → 180
Injection port		200
Detector		250

Detection: flame ionisation.

Injection: 3 µL

Limit:
- *impurity D*: not more than the area of the principal peak in the chromatogram obtained with the reference solution (0.1 per cent).

Related substances. Liquid chromatography (*2.2.29*).

Test solution. Dissolve 25 mg of the substance to be examined in the mobile phase and dilute to 10.0 mL with the mobile phase.

Reference solution (a). Dilute 1.0 mL of the test solution to 50.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 10.0 mL with the mobile phase.

Reference solution (b). Dissolve 5 mg of *foscarnet impurity B CRS* in the mobile phase, add 2.0 mL of the test solution and dilute to 50.0 mL with the mobile phase.

Reference solution (c). Dissolve the contents of a vial of *foscarnet impurity mixture CRS* (impurities A and C) in 1.0 mL of mobile phase.

Column:
- *size*: *l* = 0.10 m, Ø = 4.6 mm;
- *stationary phase*: *octadecylsilyl silica gel for chromatography R* (3 µm).

Mobile phase: dissolve 3.22 g of *sodium sulfate decahydrate R* in *water R*, add 3 mL of *glacial acetic acid R* and 6 mL of a 44.61 g/L solution of *sodium pyrophosphate R* and dilute to 1000 mL with *water R* (solution A); dissolve 3.22 g of *sodium sulfate decahydrate R* in *water R*, add 6.8 g of *sodium acetate R* and 6 mL of a 44.61 g/L solution of *sodium pyrophosphate R* and dilute to 1000 mL with *water R* (solution B). Mix about 700 mL of solution A and about 300 mL of solution B to obtain a solution of pH 4.4. To 1000 mL of this solution, add 0.25 g of *tetrahexylammonium hydrogen sulfate R* and 100 mL of *methanol R*.

Flow rate: 1.0 mL/min.

Detection: spectrophotometer at 230 nm.

Injection: 40 µL.

Run time: 2.5 times the retention time of foscarnet.

Identification of impurities: use the chromatogram supplied with *foscarnet impurity mixture CRS* and the chromatogram obtained with reference solution (c) to identify the peaks due to impurities A and C; use the chromatogram obtained with reference solution (b) to identify the peak due to impurity B.

Relative retention with reference to foscarnet (retention time = about 5 min): impurity A = about 0.7; impurity B = about 1.5; impurity C = about 2.0.

System suitability: reference solution (b):
- *resolution*: minimum 7.0 between the peaks due to foscarnet and impurity B.

Limits:
- *impurities A, B, C*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 per cent);
- *unspecified impurities*: for each impurity, not more than 0.25 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent);
- *total*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (a) (0.4 per cent);
- *disregard limit*: 0.2 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.04 per cent); disregard any peak with a relative retention time less than 0.6.

Phosphate and phosphite. Liquid chromatography (*2.2.29*).

Test solution. Dissolve 60.0 mg of the substance to be examined in *water R* and dilute to 25.0 mL with the same solvent.

Reference solution (a). Dissolve 28 mg of *sodium dihydrogen phosphate monohydrate R* in *water R* and dilute to 100 mL with the same solvent.