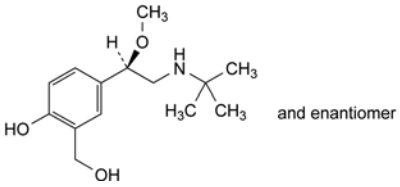
1 mL of *0.1 M perchloric acid* is equivalent to 23.93 mg of $C_{13}H_{21}NO_3$.

STORAGE

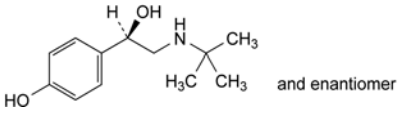
Protected from light.

IMPURITIES

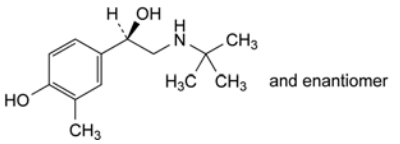
Specified impurities: A, B, C, D, E, F, G, H, I, J.



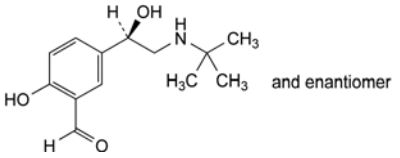
A. 5-[(1*RS*)-2-[(1,1-dimethylethyl)amino]-1-methoxyethyl]-2-hydroxyphenyl]methanol,



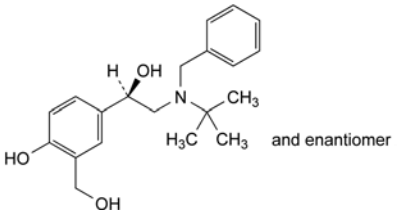
B. (1*RS*)-2-[(1,1-dimethylethyl)amino]-1-(4-hydroxyphenyl)ethanol,



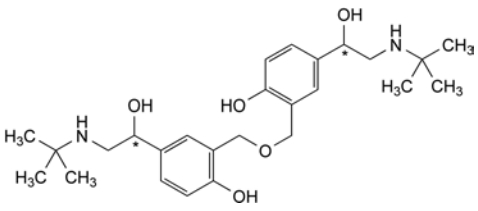
C. (1*RS*)-2-[(1,1-dimethylethyl)amino]-1-(4-hydroxy-3-methylphenyl)ethanol,



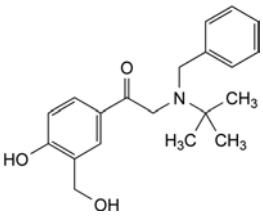
D. 5-[(1*RS*)-2-[(1,1-dimethylethyl)amino]-1-hydroxyethyl]-2-hydroxybenzaldehyde,



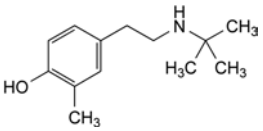
E. (1*RS*)-2-[benzyl(1,1-dimethylethyl)amino]-1-[4-hydroxy-3-(hydroxymethyl)phenyl]ethanol,



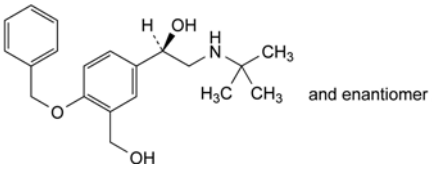
F. 1,1′-[oxybis[methylene(4-hydroxy-1,3-phenylene)]]bis[2-[(1,1-dimethylethyl)amino]ethanol],



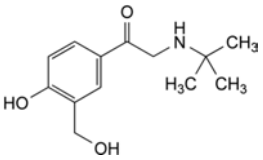
G. 2-[benzyl(1,1-dimethylethyl)amino]-1-[4-hydroxy-3-(hydroxymethyl)phenyl]ethanone,



H. 4-[2-[(1,1-dimethylethyl)amino]ethyl]-2-methylphenol,



I. (1*RS*)-2-[(1,1-dimethylethyl)amino]-1-[4-(benzyloxy)-3-(hydroxymethyl)phenyl]ethanol,

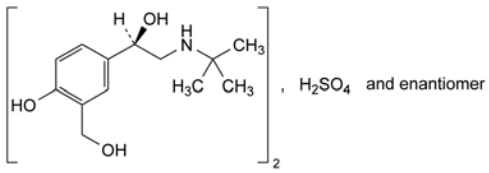


J. 2-[(1,1-dimethylethyl)amino]-1-[4-hydroxy-3-(hydroxymethyl)phenyl]ethanone (salbutamone).

07/2010:0687
corrected 7.0

SALBUTAMOL SULFATE

Salbutamoli sulfas



$C_{26}H_{44}N_2O_{10}S$ M_r 576.7
[51022-70-9]

DEFINITION

Bis[(1*RS*)-2-[(1,1-dimethylethyl)amino]-1-[4-hydroxy-3-(hydroxymethyl)phenyl]ethanol] sulfate.

Content: 98.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance: white or almost white, crystalline powder.

Solubility: freely soluble in water, practically insoluble or very slightly soluble in ethanol (96 per cent) and in methylene chloride.

It shows polymorphism (*5.9*).

IDENTIFICATION

First identification: B, E.

Second identification: A, C, D, E.

A. Ultraviolet and visible absorption spectrophotometry (*2.2.25*).

Test solution. Dissolve 80.0 mg in a 10 g/L solution of *hydrochloric acid R* and dilute to 100.0 mL with the same acid. Dilute 10.0 mL of the solution to 100.0 mL with a 10 g/L solution of *hydrochloric acid R*.

Spectral range: 230-350 nm.

Absorption maximum: at 276 nm.

Specific absorbance at the absorption maximum: 55 to 64.

B. Infrared absorption spectrophotometry (*2.2.24*).

Comparison: *salbutamol sulfate CRS*.

If the spectra obtained show differences, dissolve the substance to be examined and the reference substance separately in *anhydrous ethanol R*. Dry the residues and record new spectra using the residues.

C. Thin-layer chromatography (*2.2.27*).

Test solution. Dissolve 12 mg of the substance to be examined in *water R* and dilute to 10 mL with the same solvent.

Reference solution. Dissolve 12 mg of *salbutamol sulfate CRS* in *water R* and dilute to 10 mL with the same solvent.

Plate: *TLC silica gel plate R*.

Mobile phase: *concentrated ammonia R, water R, ethyl acetate R, 2-propanol R, methyl isobutyl ketone R* (3:18:35:45:50 *V/V/V/V/V*).

Application: 1 µL.

Development: over 2/3 of the plate.

Drying: in air.

Detection: spray with a 1 g/L solution of *methylbenzothiazolone hydrazone hydrochloride R* in a 90 per cent *V/V* solution of *methanol R*, followed by a 20 g/L solution of *potassium ferricyanide R* in a mixture of 1 volume of *concentrated ammonia R1* and 3 volumes of *water R*, followed by a further spraying with a 1 g/L solution of *methylbenzothiazolone hydrazone hydrochloride R* in a 90 per cent *V/V* solution of *methanol R*.

Results: the principal spot in the chromatogram obtained with the test solution is similar in position, colour and size to the principal spot in the chromatogram obtained with the reference solution.

D. Dissolve about 10 mg in 50 mL of a 20 g/L solution of *disodium tetraborate R*. Add 1 mL of a 30 g/L solution of *aminopyrazolone R*, 10 mL of *methylene chloride R* and 10 mL of a 20 g/L solution of *potassium ferricyanide R*. Shake and allow to separate. An orange-red colour develops in the methylene chloride layer.

E. It gives reaction (a) of sulfates (*2.3.1*).

TESTS

Solution S. Dissolve 0.250 g in *carbon dioxide-free water R* and dilute to 25.0 mL with the same solvent.

Appearance of solution. Solution S is clear (*2.2.1*) and not more intensely coloured than reference solution BY_6 (*2.2.2, Method II*).

Optical rotation (*2.2.7*): −0.10° to + 0.10°, determined on solution S.

Acidity or alkalinity. To 10 mL of solution S add 0.15 mL of *methyl red solution R* and 0.2 mL of *0.01 M sodium hydroxide*. The solution is yellow. Not more than 0.4 mL of *0.01 M hydrochloric acid* is required to change the colour of the indicator to red.

Related substances. Liquid chromatography (*2.2.29*).

Test solution. Dissolve 20.0 mg of the substance to be examined in mobile phase A and dilute to 50.0 mL with mobile phase A.

Reference solution (a). Dissolve 3.0 mg each of *salbutamol impurity D CRS* and 3.0 mg of *salbutamol impurity F CRS* in mobile phase A and dilute to 50.0 mL with mobile phase A. Dilute 2.0 mL of this solution to 100.0 mL with mobile phase A.

Reference solution (b). Dilute 1.0 mL of the test solution to 100.0 mL with mobile phase A. Dilute 1.0 mL of this solution to 10.0 mL with mobile phase A.

Reference solution (c). With the aid of ultrasounds, dissolve the contents of a vial of *salbutamol impurity J CRS* in 1.0 mL of the test solution.

Reference solution (d). Dissolve 1 mg of *salbutamol impurity D CRS* in mobile phase A and dilute to 100.0 mL with mobile phase A.

Reference solution (e). Dissolve 10 mg of *salbutamol sulfate for system suitability CRS* (containing impurities C, F, N and O) in mobile phase A, add 1.0 mL of reference solution (d) and dilute to 50.0 mL with mobile phase A.

Column:

- *size*: *l* = 0.15 m, Ø = 4.6 mm;
- *stationary phase*: spherical *end-capped octylsilyl silica gel for chromatography R* (3 µm);
- *temperature*: 30 °C.

Mobile phase:

- *mobile phase A*: dissolve 3.45 g of *sodium dihydrogen phosphate monohydrate R* in 900 mL of a 0.05 per cent *V/V* solution of *triethylamine R*, adjust to pH 3.0 with *dilute phosphoric acid R* and dilute to 1000 mL with a 0.05 per cent *V/V* solution of *triethylamine R*;
- *mobile phase B*: *methanol R, acetonitrile R* (35:65 *V/V*);

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 5	95	5
5 - 30	95 → 10	5 → 90

Flow rate: 1.0 mL/min.

Detection: spectrophotometer at 273 nm.

Injection: 20 µl of the test solution and reference solutions (a), (b), (c) and (e).

Relative retention with reference to salbutamol (retention time = about 7 min): impurity J = about 0.9; impurity C = about 1.6; impurity D = about 1.69; impurity N = about 1.71; impurity F = about 1.77; impurity O = about 1.82.

Identification of impurities: use the chromatogram obtained with reference solution (e) to identify the peaks due to impurities C, D, F, N and O; use the chromatogram obtained with reference solution (c) to identify the peak due to impurity J.

System suitability:

- *peak-to-valley ratio*: minimum 4, where H_p = height above the baseline of the peak due to impurity D and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to impurity N in the chromatogram obtained with reference solution (e);
- *resolution*: minimum 1.5 between the peaks due to impurity J and salbutamol in the chromatogram obtained with the reference solution (c).

Limits:

- *impurities D, F*: for each impurity, not more than the area of the corresponding peak in the chromatogram obtained with reference solution (a) (0.3 per cent);
- *impurities C, N, O*: for each impurity, not more than twice the area of the principal peak in the chromatogram obtained with reference solution (b) (0.2 per cent);
- *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.10 per cent);
- *total*: not more than 9 time the area of the principal peak in the chromatogram obtained with reference solution (b) (0.9 per cent);
- *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent).

Boron: maximum 50 ppm.

Test solution. To 50 mg of the substance to be examined add 5 mL of a solution containing 13 g/L of *anhydrous sodium carbonate R* and 17 g/L of *potassium carbonate R*. Evaporate to dryness on a water-bath and dry at 120 °C. Ignite the residue rapidly until the organic matter has been destroyed, allow to cool and add 0.5 mL of *water R* and 3.0 mL of a freshly prepared 1.25 g/L solution of *curcumin R* in *glacial acetic acid R*. Warm gently to effect solution, allow to cool and add 3.0 mL of a mixture prepared by adding 5 mL of *sulfuric acid R*, slowly and with stirring, to 5 mL of *glacial acetic acid R*. Mix and allow to stand for 30 min. Dilute to 100.0 mL with *ethanol (96 per cent) R*, filter and use the filtrate.

Reference solution. Dissolve 0.572 g of *boric acid R* in 1000.0 mL of *water R*. Dilute 1.0 mL of the solution to 100.0 mL with *water R*. To 2.5 mL of this solution add 5 mL of a solution containing 13 g/L of *anhydrous sodium carbonate R* and 17 g/L of *potassium carbonate R*, and treat this mixture in the same manner as the test solution.

Measure the absorbance (*2.2.25*) of the test solution and of the reference solution at the absorption maximum at about 555 nm. The absorbance of the test solution is not greater than that of the reference solution.

Loss on drying (*2.2.32*): maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C.

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

ASSAY

Dissolve 0.400 g in 5 mL of *anhydrous formic acid R* and add 35 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 57.67 mg of $C_{26}H_{44}N_2O_{10}S$.

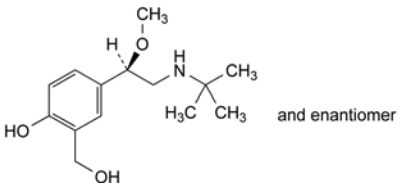
STORAGE

Protected from light.

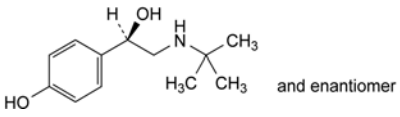
IMPURITIES

Specified impurities: *C, D, F, N, O.*

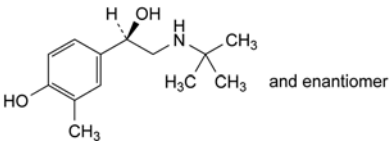
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph *Substances for pharmaceutical 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*): *A, B, E, G, I, J, K, L, M.*



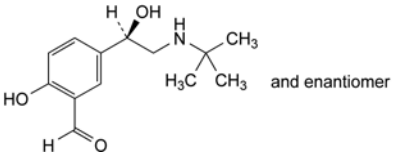
A. [5-[(1*RS*)-2-[(1,1-dimethylethyl)amino]-1-methoxyethyl]-2-hydroxyphenyl]methanol,



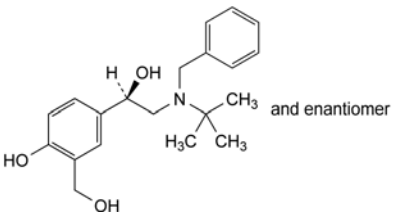
B. (1*RS*)-2-[(1,1-dimethylethyl)amino]-1-(4-hydroxyphenyl)ethanol,



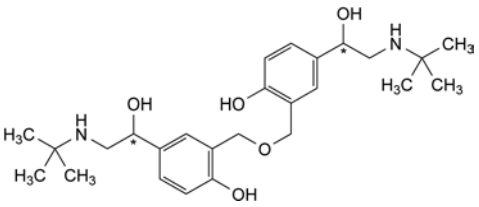
C. (1*RS*)-2-[(1,1-dimethylethyl)amino]-1-(4-hydroxy-3-methylphenyl)ethanol,



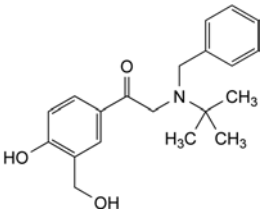
D. 5-[(1*RS*)-2-[(1,1-dimethylethyl)amino]-1-hydroxyethyl]-2-hydroxybenzaldehyde,



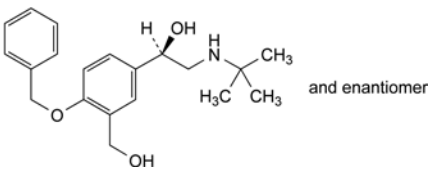
E. (1*RS*)-2-[benzyl(1,1-dimethylethyl)amino]-1-[4-hydroxy-3-(hydroxymethyl)phenyl]ethanol,



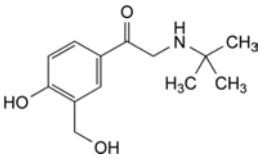
F. 1,1′-[oxybis[methylene(4-hydroxy-1,3-phenylene)]]bis[2-[(1,1-dimethylethyl)amino]ethanol],



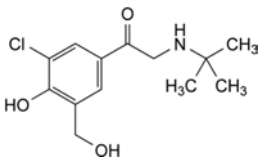
G. 2-[benzyl(1,1-dimethylethyl)amino]-1-[4-hydroxy-3-(hydroxymethyl)phenyl]ethanone,



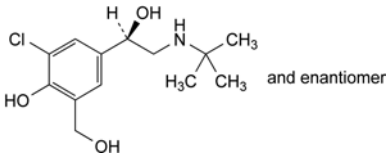
I. (1*RS*)-2-[(1,1-dimethylethyl)amino]-1-[4-(benzyloxy)-3-(hydroxymethyl)phenyl]ethanol,



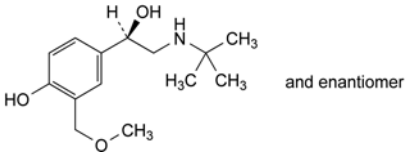
J. 2-[(1,1-dimethylethyl)amino]-1-[4-hydroxy-3-(hydroxymethyl)phenyl]ethanone (salbutamone),



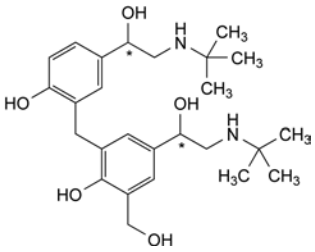
K. 2-[(1,1-dimethylethyl)amino]-1-[3-chloro-4-hydroxy-5-(hydroxymethyl)phenyl]ethanone,



L. (1*RS*)-2-[(1,1-diméthyléthyl)amino]-1-[3-chloro-4-hydroxy-5-(hydroxyméthyl)phényl]ethanol,



M. (1*RS*)-2-[(1,1-dimethylethyl)amino]-1-[4-hydroxy-3-(methoxymethyl)phenyl]ethanol,



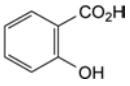
N. 2-[(1,1-dimethylethyl)amino]-1-[3-[[5-[2-[(1,1-dimethylethyl)amino]-1-hydroxyethyl]-2-hydroxyphenyl]methyl]-4-hydroxy-5-(hydroxymethyl)phenyl]ethanol,

O. unknown structure.

01/2008:0366
corrected 6.0

SALICYLIC ACID

Acidum salicylicum



$C_7H_6O_3$ M_r 138.1
[69-72-7]

DEFINITION

2-Hydroxybenzenecarboxylic acid.

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

CHARACTERS

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

Solubility: slightly soluble in water, freely soluble in ethanol (96 per cent), sparingly soluble in methylene chloride.

IDENTIFICATION

First identification: A, B.

Second identification: A, C.

A. Melting point (*2.2.14*): 158 °C to 161 °C.

B. Infrared absorption spectrophotometry (*2.2.24*).
Comparison: *salicylic acid CRS.*

C. Dissolve about 30 mg in 5 mL of *0.05 M sodium hydroxide*, neutralise if necessary and dilute to 20 mL with *water R*. 1 mL of the solution gives reaction (a) of salicylates (*2.3.1*).

TESTS

Solution S. Dissolve 2.5 g in 50 mL of boiling *distilled water R*, cool and filter.

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

Dissolve 1 g in 10 mL of *ethanol (96 per cent) R*.

Related substances. Liquid chromatography (*2.2.29*).

Test solution. Dissolve 0.50 g of the substance to be examined in the mobile phase and dilute to 100.0 mL with the mobile phase.

Reference solution (a). Dissolve 10 mg of *phenol R* (impurity C) in the mobile phase and dilute to 100.0 mL with the mobile phase.

Reference solution (b). Dissolve 5 mg of *salicylic acid impurity B CRS* in the mobile phase and dilute to 20.0 mL with the mobile phase.

Reference solution (c). Dissolve 50 mg of *4-hydroxybenzoic acid R* (impurity A) in the mobile phase and dilute to 100.0 mL with the mobile phase.

Reference solution (d). Dilute 1.0 mL of reference solution (a) to 10.0 mL with the mobile phase.

Reference solution (e). Dilute a mixture of 1.0 mL of each of reference solutions (a), (b) and (c) to 10.0 mL with the mobile phase.

Reference solution (f). Dilute a mixture of 0.1 mL of each of reference solutions (a), (b) and (c) to 10.0 mL with the mobile phase.

Column:
- *size*: *l* = 0.15 m, Ø = 4.6 mm;
- *stationary phase*: non-deactivated *octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase: *glacial acetic acid R, methanol R, water R* (1:40:60 *V/V/V*).

Flow rate: 0.5 mL/min.

Detection: spectrophotometer at 270 nm.

Injection: 10 µL of the test solution and reference solutions (d), (e) and (f).

Relative retention with reference to impurity C: impurity A = about 0.70; impurity B = about 0.90.

System suitability: reference solution (e):
- the 3rd peak in the chromatogram corresponds to the peak due to phenol in the chromatogram obtained with reference solution (d);
- *resolution*: minimum 1.0 between the peaks due to impurities B and C; if necessary, adjust the quantity of acetic acid in the mobile phase.

Limits:
- *impurity A*: not more than the area of the corresponding peak in the chromatogram obtained with reference solution (f) (0.1 per cent);
- *impurity B*: not more than the area of the corresponding peak in the chromatogram obtained with reference solution (f) (0.05 per cent);
- *impurity C*: not more than the area of the corresponding peak in the chromatogram obtained with reference solution (f) (0.02 per cent);
- *any other impurity*: for each impurity, not more than the area of the peak due to impurity B in the chromatogram obtained with reference solution (f) (0.05 per cent);
- *total*: not more than twice the area of the peak due to impurity A in the chromatogram obtained with reference solution (f) (0.2 per cent);
- *disregard limit*: 0.01 times the area of the principal peak in the chromatogram obtained with reference solution (f).