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Notes: Revised monograph. Related substances: Revised method. Uniformity of Delivered Dose: New method.	

Salbutamol Pressurised Inhalation, Suspension

Salbutamol Pressurised Inhalation

Salbutamol Preparations

Action and use
Beta$_2$-adrenoceptor agonist; bronchodilator.

DEFINITION

Salbutamol Pressurised Inhalation, Suspension is a suspension of either Salbutamol or Salbutamol Sulfate in a suitable liquid in a pressurised container fitted with a metering dose valve.

The pressurised inhalation, suspension complies with the requirements stated under Preparations for Inhalation and with the following requirements.

PRODUCTION

The size of aerosol particles to be inhaled is controlled so that a consistent portion is deposited in the lungs. The fine-particle characteristics of preparations for inhalation are determined using the method described in Appendix XII C7. Preparations for inhalation: Aerodynamic Assessment of Fine Particles. The test and limits should be agreed with the competent authority.

The water content is controlled to ensure the performance of the product as justified and authorised by the competent authority.

Content of salbutamol, $C_{13}H_{21}NO_3$
80.0 to 120.0% of the stated amount.

IDENTIFICATION

The *infrared absorption spectrum*, Appendix II A, in the range 1650 to 400 cm^{-1} is concordant with the *reference spectrum* of either salbutamol (*RS 314*) or salbutamol sulfate (*RS 315*), as appropriate. Examine the substance as a dispersion in *potassium bromide* prepared in the following manner. Discharge the inhaler a sufficient number of times into a mortar to obtain 2 mg of Salbutamol, grind the residue thoroughly with 0.1 g of *potassium bromide*, add a further 0.2 g of *potassium bromide* and mix thoroughly.

TESTS

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in the mobile phase.

Solution A 45 volumes methanol and 55 volumes of 0.1% *phosphoric acid*.

Solution B Dissolve 1.442 g *sodium dodecyl sulfate* in 980 mL *water*, add 6.8 mL of *phosphoric acid 85%* and adjust to pH 2.5 with sufficient *trimethylamine*.

(1) Freeze the pressurised container and carefully open the canister. Empty the contents into a 100-mL flask and rinse the canister with 10 mL of solution A and collect the washing in the flask. Repeat the wash step a further 3 times, adding the washings to the flask. Dilute to volume with solution A and dilute if necessary to make a solution containing 0.004% w/v of salbutamol sulfate.

(2) Dilute 1 volume of solution (1) to 100 volumes.

(3) 0.00086% w/v of *salbutamol sulfate BPCRS* and 0.0012% w/v of *2-tert-butylamino-1-(4-hydroxy-3-methylphenyl)ethanol BPCRS* in solution A.

(4) Dilute 1 volume of solution (2) to 10 volumes with solution A.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 4.6 mm) packed with spherical *end-capped octylsilyl silica gel for chromatography* (5 µm) (Supelco LC-18 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 2 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 278 nm.

(f) Inject 20 µL of each solution.

(g) Allow the chromatography to proceed for 4 times the retention time of salbutamol.

When the chromatograms are recorded under the prescribed conditions, the relative retention with reference to salbutamol sulfate (retention time about 4.1 minutes) for 2-tert-butylamino-1-(4-hydroxy-3-methylphenyl)ethanol is about 2.4.

MOBILE PHASE

45 volumes of *methanol* and 55 volumes of solution B.

SYSTEM SUITABILITY

TBC

LIMITS

In the chromatogram obtained with solution (1):

the area of any *secondary peak* is not greater than 0.5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.5%);

the sum of the areas of all *secondary peaks* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (1.0%).

Disregard any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (5) (0.1%).

Uniformity of delivered dose

Complies with the requirements stated under Pressurised Metered-dose Preparations for Inhalation using the following method of analysis. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

Solution A 45 volumes methanol and 55 volumes of 0.1% *phosphoric acid*.

Solution B Dissolve 1.442 g *sodium dodecyl sulfate* in 980 mL *water*, add 6.8 mL of *phosphoric acid 85%* and adjust to pH 2.5 with sufficient *trimethylamine*.

(1) Collect single doses of the preparation being examined using the procedure described under Pressurised Metered-dose Preparations for Inhalation, Uniformity of delivered dose and dissolve the collected dose in sufficient solution A to produce a solution containing the equivalent of 0.00036% w/v of Salbutamol Sulfate.

(2) 0.00043% w/v of *salbutamol sulfate BPCRS* in the mobile phase.

(3) 0.00086% w/v of *salbutamol sulfate BPCRS* and 0.0012% w/v of *2-tert-butylamino-1-(4-hydroxy-3-methylphenyl)ethanol BPCRS* in solution A.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm x 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Supelco LC-18 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 2 mL per minute.

(d) Use an ambient column temperature

(e) Use a detection wavelength of 225 nm.

(f) Inject 20 µL of each solution

MOBILE PHASE

45 volumes of *methanol* and 55 volumes of Solution B.

When the chromatograms are recorded under the prescribed conditions, the retention time relative to salbutamol sulfate (retention time about 4.1 minutes) for 2-tert-butylamino-1-(4-hydroxy-3-methylphenyl)ethanol is about 2.4.

SYSTEM SUITABILITY

The test is not valid unless the relative standard deviation of the peak areas of *2-tert-butylamino-1-(4-hydroxy-3-methylphenyl)ethanol BPCRS* is not more than 1.5%.

DETERMINATION OF CONTENT

Calculate the content of Salbutamol, $C_{13}H_{21}NO_3$ per aliquot of solvent using the declared content of $C_{13}H_{21}NO_3$ in *salbutamol sulfate BPCRS*. Repeat the procedure as described under Pressurised Metered-dose Preparations for Inhalation, Uniformity of delivered dose.

Salbutamol ketone

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in *water*.

(1) Dilute a quantity of the contents of the inhaler with sufficient *water* to produce a solution containing the equivalent of 0.050% w/v of Salbutamol.

(2) 0.00025% w/v of *salbutamol ketone impurity BPCRS*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *end-capped octylsilyl silica gel for chromatography* (5 µm) (Hypersil BDS C8 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use a column temperature of 30°.

(e) Use a detection wavelength of 276 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

Mobile phase A A mixture of 1.5 volumes of *propan-2-ol* and 98.5 volumes of 0.1M *ammonium acetate* adjusted to pH 4.5 with *glacial acetic acid*.

Mobile phase B *propan-2-ol*.

Time (minutes)	Mobile phase A % v/v	Mobile phase B % v/v
0 – 5	100	0
5 – 20	100 → 86	0 → 14
20 – 30	86	14

LIMITS

In the chromatogram obtained with solution (1):

the area of any peak corresponding to salbutamol ketone is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.5%).

ASSAY

Use the average of the individual results determined in the test for Uniformity of delivered dose.

LABELLING

The label states the content of active ingredient in terms of the equivalent amount of salbutamol.