Salbutamol Pressurised Inhalation, Suspension

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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\textsubscript{13}H\textsubscript{17}NO\textsubscript{3}
83.0 to 115.0\% of the stated delivered dose (ex-actuator).

IDENTIFICATION
The infrared absorption spectrum, Appendix II A, in the range 1650 to 400 cm\textsuperscript{-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
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.

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 methanol to produce a solution containing the equivalent of 0.000075\% w/v of Salbutamol.

2) 0.00018\% w/v of salbutamol sulfate BPCRS in methanol.

CHROMATOGRAPHIC CONDITIONS
(a) Use a stainless steel column (10 cm x 3 mm) packed with octadecylsilyl silica gel for chromatography (5 μm) (Spherisorb ODS is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 0.85 mL per minute.
(d) Use a column temperature of 50º.
(e) Use a detection wavelength of 276 nm.
(f) Inject 150 μL of each solution.

MOBILE PHASE
762 volumes of methanol and 238 volumes of 0.1% w/v of ammonium acetate solution.

DETERMINATION OF CONTENT
Calculate the content of Salbutamol, C\textsubscript{13}H\textsubscript{17}NO\textsubscript{3} per aliquot of solvent using the declared content of C\textsubscript{13}H\textsubscript{17}NO\textsubscript{3} in salbutamol sulfate BPCRS. Repeat the procedure as described under Pressurised Metered-dose Preparations for Inhalation, Uniformity of delivered dose.

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

1) Shake a quantity of the pressurised inhalation containing 5 mg of Salbutamol with 25 mL of water to produce a solution containing 0.02% w/v of salbutamol.

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

3) 0.005% w/v of salbutamol sulfate for system suitability EPCRS, 0.005% w/v of 2-tert-butylamino-1-(4-hydroxy-3-methylphenyl)ethanol BPCRS (impurity C) and 0.00075% w/v of salbutamol ketone impurity BPCRS (impurity J) in water.

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

CHROMATOGRAPHIC CONDITIONS
(a) Use a stainless steel column (25 cm x 4.6 mm) packed with end-capped octadecyl silica gel for chromatography (5 μm) (Hypersil 100 C8 is suitable).

(b) Use gradient elution and the mobile phase described below.
(c) Use a flow rate of 1.0 mL per minute.
(d) Use a column temperature of 30º.
(e) Use a detection wavelength of 273 nm.
(f) Inject 20 µL of each solution.

**MOBILE PHASE**

*Mobile phase A* 0.1M ammonium acetate, adjusted to pH 4.5 with acetic acid

*Mobile phase B* isopropranol.

<table>
<thead>
<tr>
<th>Time (Min)</th>
<th>Mobile Phase A (% v/v)</th>
<th>Mobile Phase B (% v/v)</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 – 5</td>
<td>96</td>
<td>4</td>
<td>isocratic</td>
</tr>
<tr>
<td>5 – 20</td>
<td>96 – 86</td>
<td>4 – 14</td>
<td>linear gradient</td>
</tr>
<tr>
<td>20 – 30</td>
<td>86</td>
<td>14</td>
<td>isocratic</td>
</tr>
<tr>
<td>30 – 31</td>
<td>86 – 96</td>
<td>14 – 4</td>
<td>linear gradient</td>
</tr>
<tr>
<td>31 – 45</td>
<td>96</td>
<td>4</td>
<td>re-equilibration</td>
</tr>
</tbody>
</table>

When the chromatograms are recorded under the prescribed conditions, the relative retentions with reference to salbutamol (retention time of about 6.4 minutes) are:
- impurity J, about 0.9;
- impurity C, about 2.1;
- impurity D, about 2.3;
- impurity N, about 2.5 and impurity F, about 2.6.

**SYSTEM SUITABILITY**

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to salbutamol and salbutamol ketone is at least 1.0.

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to impurity N and impurity F is at least 1.2.

**LIMITS**

Use the chromatogram obtained with solution (3) to identify the peaks due to impurities C, D, F, J and N in the chromatogram obtained from solution (1). Multiply the area of any peak corresponding to impurity C, F, J and N by a correction factor of 1.7, 0.6, 0.2 and 1.4 respectively.

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 1.2 times the area of the principal peak in the chromatogram obtained with solution (2) (1.2%).

Disregard any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (4) (0.1%).

**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.

**IMPURITIES**

The impurities limited by the requirements of this monograph include those listed under Salbutamol.