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Furosemide Tablets

General Notices

Details for the public consultation of this monograph are as follows:

<table>
<thead>
<tr>
<th>EAG MC2</th>
<th>Medicinal Chemicals 2</th>
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| Deadline for Comment | 31st September 2019 |
| Target Publication Date (subject to change) | BP 2021 |
| Notes: | Monograph Revision |
| Related Substances: Use of new EPCRS for peak identification. |
| Adjustment to Impurity limits based on ICH guidelines. |
| Assay: Introduction of HPLC assay, replacing Assay by UV absorbance. |

Action and use

Loop diuretic.

DEFINITION

Furosemide Tablets contain Furosemide.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of furosemide, C_{12}H_{11}ClN_{2}O_{5}S

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. The light absorption, Appendix II B, in the range 220 to 320 nm of the final solution obtained in the Assay exhibits two maxima, at 228 nm and 271 nm.

B. In the test for Assay, the principal peak in the chromatogram obtained with solution (1) shows a peak with the same retention time as the principal peak in the chromatogram obtained with solution (2).

TESTS

Dissolution
Comply with the dissolution test for tablets and capsules, Appendix XII B1.

TEST CONDITIONS

(a) Use Apparatus 2, rotating the paddle at 50 revolutions per minute.
(b) Use 900 mL of phosphate buffer pH 5.8, at a temperature of 37°, as the medium.

PROCEDURE

(1) After 45 minutes withdraw a sample of the medium and measure the absorbance of the filtered sample, suitably diluted with the dissolution medium if necessary, at the maximum at 277 nm, Appendix II B, using dissolution medium in the reference cell.
(2) Measure the absorbance of a 0.001% w/v solution of furosemide BPCRS in the dissolution medium using dissolution medium in the reference cell.

DETERMINATION OF CONTENT

Calculate the total content of furosemide, C\textsubscript{12}H\textsubscript{11}ClN\textsubscript{2}O\textsubscript{5}S, in the medium from the absorbances obtained and using the declared content of C\textsubscript{12}H\textsubscript{11}ClN\textsubscript{2}O\textsubscript{5}S in furosemide BPCRS.

LIMITS

The amount of furosemide released is not less than 75% (Q) of the stated amount.

Related substances

Carry out the method for liquid chromatography, Appendix III D, using the following solutions. Prepare the solutions immediately before use and protect from light.

(1) Dissolve a quantity of the powdered tablets containing 20 mg of Furosemide in sufficient mobile phase to produce 50 mL and mix with the aid of ultrasound for 15 minutes.
(2) Dilute 1 volume of solution (1) to 200 volumes with the mobile phase.
(3) 0.00008% w/v of each of furosemide BPCRS and furosemide impurity A EPCRS in the mobile phase.
(4) 0.04% w/v of furosemide for peak identification EPCRS in the mobile phase.
(5) Dilute 1 volume of solution (2) to 5 volumes with the mobile phase.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column 25 cm × 4.6 mm packed with octylsilyl silica gel for chromatography (5 µm) (symmetry 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 an ambient column temperature.
(e) Use a detection wavelength of 238 nm.
(f) Inject 100 µL of each solution.
(g) Allow the chromatography to proceed for 3 times the retention time of furosemide.

MOBILE PHASE

30 volumes of propan-1-ol and 70 volumes of a solution of 0.2% w/v potassium dihydrogen phosphate and 0.25% w/v cetrimide in water adjusted to pH 7.0 using 6M ammonia.

When the chromatograms are recorded under the prescribed conditions, the retention times relative to furosemide (retention time about 9 minutes) are: impurity C, about 0.5; impurity A, about 0.8 and impurity D, about 1.5.
SYSTEM SUITABILITY

Identify the peak due to impurity D using the relative retention time, multiply the area of this peak by 2.0.

The test is not valid unless, in the chromatogram obtained with solution (3), the resolution between the peaks due to impurity A and furosemide is at least 4.0.

LIMITS

In the chromatogram obtained with solution (1):

The area of any peak corresponding to 4-chloro-5-sulfamoylanthranilic acid (impurity C) is not greater than 1.6 times the area of the peak in the chromatogram obtained with solution (2) (0.8%);

the area of any peak corresponding to Impurity D is not greater than twice the area of the principal peak in the chromatogram obtained with solution (5) (0.2%);

the area of any other secondary peak is not greater than twice the area of the principal peak in the chromatogram obtained with solution (5) (0.2%);

the sum of the areas of any other secondary peaks is not greater than the area of the peak in the chromatogram obtained with solution (2) (0.5%).

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

ASSAY

Weigh and powder 20 tablets. Carry out the method for liquid chromatography, Appendix III D, using the following solutions. Prepare the solutions immediately before use and protect from light.

(1) Dissolve a quantity of the powdered tablets containing 20 mg of Furosemide in sufficient mobile phase to produce 50 mL and mix with the aid of ultrasound for 15 minutes.

(2) 0.01% w/v of furosemide BPCRS in mobile phase.

(3) 0.00025% w/v each of furosemide BPCRS and furosemide impurity A EPCRS in mobile phase.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions stated under Related substances may be used, using an injection volume of 20 µl.

SYSTEM SUITABILITY

The test is not valid unless the resolution between the peaks due to impurity A and furosemide is at least 4.

DETERMINATION OF CONTENT

Calculate the content of furosemide, C_{12}H_{11}ClN_{2}O_{5}S, in the tablets from the chromatograms obtained and using the declared content of C_{12}H_{11}ClN_{2}O_{5}S, in furosemide BPCRS.

IMPURITIES

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