Edition: BP 2025 (Ph. Eur. 11.6 update)

Sodium Valproate Gastro-resistant Tablets

General Notices

Gastro-resistant Sodium Valproate Tablets

Sodium Valproate Gastro-resistant Tablets from different manufacturers, whilst complying with the requirements of the monograph, may not be interchangeable.

Action and use

Antiepileptic.

DEFINITION

Sodium Valproate Gastro-resistant Tablets contain Sodium Valproate. They are made gastro-resistant by enteric-coating or by other means.

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

Content of sodium valproate, $C_8H_{15}NaO_2$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Shake a quantity of the powdered tablets containing 0.5 g of Sodium Valproate with 10 mL of *water* and centrifuge. Acidify 5 mL of the supernatant liquid with 2M *sulfuric acid*, shake with 25 mL of *dichloromethane* and wash the dichloromethane layer with 5 mL of *water*. Dry by shaking with *anhydrous sodium sulfate*, filter and evaporate the dichloromethane to dryness. The *infrared absorption spectrum* of a thin film of the residue, Appendix II A, is concordant with the *reference spectrum* of valproic acid (*RS 431*).
B. Shake a quantity of the powdered tablets containing 0.25 g of Sodium Valproate with 3 mL of *water* and centrifuge. To 2 mL of the supernatant liquid add 0.5 mL of a 10% w/v solution of *cobalt(II) nitrate*. A purple precipitate is produced which is soluble in *dichloromethane*.

TESTS

Dissolution

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

TEST CONDITIONS

First stage

(a) Use Apparatus 1, rotating the basket at 100 revolutions per minute.
(b) Use 900 mL of *0.1M hydrochloric acid*, at a temperature of 37°, as the medium.

PROCEDURE

(1) After 2 hours, withdraw a sample of the medium and filter.
(2) 0.001% w/v of *sodium valproate BPCRS* in *0.1M hydrochloric acid*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (30 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (µBondapak C18 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 220 nm.
(f) Inject 50 µL of each solution.

MOBILE PHASE

45 volumes of a 0.32% w/v solution of *potassium dihydrogen orthophosphate* adjusted to pH 3.0 with *orthophosphoric acid* and 55 volumes of *acetonitrile*.

DETERMINATION OF CONTENT

Calculate the total content of sodium valproate, $C_8H_{15}NaO_2$, in the medium using the declared content of $C_8H_{15}NaO_2$ in *sodium valproate BPCRS*.

LIMITS

The amount of sodium valproate released is not more than 5% of the stated amount.

Final stage

(a) Use Apparatus 1, rotating the basket at 100 revolutions per minute.
(b) Replace the *0.1M hydrochloric acid* in the vessel with 900 mL of *phosphate buffer pH 6.8*, previously held at 37°, as the medium.

PROCEDURE

(1) After 60 minutes, withdraw a sample of the medium and filter. Use the filtrate diluted, if necessary, to give a solution expected to contain 0.002% w/v of Sodium Valproate.
(2) 0.002% w/v solution of *sodium valproate BPCRS* in the dissolution medium.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under the first stage may be used.

DETERMINATION OF CONTENT

Calculate the total content of sodium valproate, $C_8H_{15}NaO_2$, in the medium using the declared content of $C_8H_{15}NaO_2$ in *sodium valproate BPCRS*.

LIMITS

The amount of sodium valproate released after the final stage is not less than 65% (Q) of the stated amount.

Related substances

Carry out the method for *gas chromatography*, Appendix III B, using the following solutions.

(1) 0.005% w/v of *octanoic acid* in *dichloromethane* (internal standard solution).
(2) Disperse a quantity of the powdered tablets containing 1 g of Sodium Valproate with 20 mL of 0.1M *sodium hydroxide*, and mix with the aid of ultrasound for 30 minutes. Centrifuge the solution and transfer 10 mL of the supernatant into a separating funnel. Mix the resulting solution with 1 mL of 2M *sulfuric acid* and add 10 mL of solution (1). Extract the mixture with three 20-mL quantities of *dichloromethane* and combine the organic layers. Dry by shaking with *anhydrous sodium sulfate*, and filter (a GF/A filter is suitable). Reduce the volume of the filtrate at a temperature not exceeding 30° and dilute to 10 mL with *dichloromethane*.
(3) Dilute 1 volume of solution (2) to 100 volumes with solution (1). Dilute 1 volume of the resulting solution to 10 volumes with solution 1.
(4) 5% w/v of *valproic acid for system suitability EPCRS* in *dichloromethane*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a fused silica capillary column (30 m × 0.53 mm) bonded with a 0.5-µm layer of *macrogol 20,000 2-nitroterephthalate* (DB-FFAP is suitable).
(b) Use *helium* as the carrier gas at 8 mL per minute.
(c) Use the temperature gradient conditions as described below.
(d) Use an injection temperature of 220°.
(e) Use a flame ionisation detector at 220°.
(f) Inject 1 µL of each solution.

(g) Use a split ratio of 1:10.

Time (Minutes)	Temperature (°C)	Comment
0-5	80	isothermal
5-15	80→150	linear gradient
15-28.3	150→190	linear gradient
28.3-30	190	isothermal
30-35	190→250	linear gradient
35-45	250	isothermal

When the chromatograms are recorded under the prescribed conditions, the relative retentions with reference to valproic acid (retention time, about 15 minutes) are: impurity K, about 0.97; octanoic acid, about 1.12.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (4), the *resolution* between the peaks due to impurity K and valproic acid is at least 2.0.

LIMITS

Using the chromatogram obtained with solution (3), calculate the ratio of the area of the peak due to valproic acid to the area of the peak due to the internal standard (*R*).

In the chromatogram obtained with solution (2):

the ratio of the area of the peak due to impurity K to the area of the peak due to the internal standard is not greater than 2*R* (0.2%);

the ratio of the area of any *secondary peak* to the area of the peak due to the internal standard is not greater than *R* (0.1%);

the ratio of the sum of the areas of any *secondary peaks* to the area of the peak due to the internal standard is not greater than 4*R* (0.4%).

Disregard any peak where the ratio of the area of any peak to the area of the peak due to the internal standard is not greater than half of *R* (0.05%) and any peak eluting after 30 minutes.

ASSAY

Weigh and powder 20 tablets. Carry out the method for *liquid chromatography*, Appendix III D using the following solutions.

Solution A Dissolve 6.8 g of *potassium dihydrogen orthophosphate* in 1000 mL of *water* and adjust to pH 6.8 with 0.2M *sodium hydroxide*.

(1) Shake and mix with the aid of ultrasound a quantity of the powdered tablets containing 0.5 g of Sodium Valproate with 50 mL of *acetonitrile R1*. Add 100 mL of solution A and mix further with the aid of ultrasound. Dilute the solution to 200 mL and filter (a 0.2-µm nylon filter is suitable). Dilute 1 volume of this solution to 5 volumes with solution A.
(2) Mix with the aid of ultrasound 50 mg of *sodium valproate BPCRS* with 5 mL of *acetonitrile R1*. Add 10 mL of solution A and mix further with the aid of ultrasound. Dilute the resulting solution to 100 mL with solution A.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *base-deactivated end-capped octadecylsilyl silica gel for chromatography* (5 µm) (Hypersil BDS C18 is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 1.0 mL per minute.
(d) Use a column temperature of 25°.
(e) Use a detection wavelength of 210 nm.
(f) Inject 20 µL of each solution.

MOBILE PHASE

50 volumes of *acetonitrile R1* and 50 volumes of a solution prepared by dissolving 1.56 g of *sodium dihydrogen orthophosphate* in 1000 mL of *water* and adjusting the pH to 2.3 with *orthophosphoric acid*.

DETERMINATION OF CONTENT

Calculate the content of $C_8H_{15}NaO_2$ in the tablets using the declared content of $C_8H_{15}NaO_2$ in *sodium valproate BPCRS*.

IMPURITIES

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