Gabapentin

C\textsubscript{9}H\textsubscript{13}NO\textsubscript{2} 171.24
Cyclohexanecarboxylic acid, 1-(aminomethyl)-
1-(Aminomethyl)cyclohexanecarboxylic acid  [60142-96-3].

» Gabapentin contains not less than 98.0 per cent and not more than 102.0 per cent of C\textsubscript{9}H\textsubscript{13}NO\textsubscript{2}, calculated on the anhydrous basis.

Packaging and storage—Preserve in well-closed containers. Store at room temperature.

USP Reference standards (11)—
USP Gabapentin RS
USP Gabapentin Related Compound A RS
C\textsubscript{9}H\textsubscript{15}NO\textsubscript{2} 153.22
USP Gabapentin Related Compound B RS
(1-Cyano-cyclohexyl)-acetic acid.
C\textsubscript{9}H\textsubscript{13}NO\textsubscript{2} 167.21
USP Gabapentin Related Compound D RS
C\textsubscript{9}H\textsubscript{15}NO\textsubscript{2} 307.43
USP Gabapentin Related Compound E RS
Carboxymethyl-cyclohexanecarboxylic acid.
C\textsubscript{9}H\textsubscript{14}O\textsubscript{3} 186.21

Identification—
A: Infrared Absorption (197K).
B: The retention time of the major peak in the chromatogram of the Assay preparation corresponds to that in the chromatogram of the Standard preparation, as obtained in the Assay.

pH (791): between 6.5 and 8.0, in a solution (1 in 50).

Water, Method I (921): not more than 0.5%.

Residue on ignition (281): not more than 0.1%.

Heavy metals, Method II (231): 0.002%.

Related compounds—
LIMIT OF EARLY ELUTING IMPURITIES—
Diluent, Buffer solution, Mobile phase, and Chromatographic system—Proceed as directed in the Assay.

Impurities solution—Dissolve suitable quantities of USP Gabapentin Related Compound A RS and USP Gabapentin Related Compound B RS in methanol to obtain a solution containing about 1.4 mg per mL and 0.84 mg per mL, respectively.

System suitability solution—Dissolve a suitable quantity of USP Gabapentin RS in Diluent, and add an appropriate volume of Impurities solution to obtain a solution containing about 14.0 mg per mL, 0.014 mg per mL, and 0.0084 mg per mL of USP Gabapentin RS, USP Gabapentin Related Compound A RS, and USP Gabapentin Related Compound B RS, respectively.

Test solution—Use the Assay preparation.

Standard solution—Dissolve a suitable quantity of USP Gabapentin Related Compound E RS in Diluent to obtain a solution having a known concentration of 8.4 \(\mu\)g per mL.

Chromatographic system (see Chromatography (621))—Prepare as directed in the Assay. Chromatograph the System suitability solution (about 20 \(\mu\)L), and record the peak responses as directed for Procedure: identify the major peaks using the relative retention times given in Table 1: the resolution, \(R\), between gabapentin related compound A and gabapentin related compound B is not less than 2.3; and the relative standard deviation for gabapentin is not more than 2.0%.

Procedure—Separately inject equal volumes (about 20 \(\mu\)L) of the Standard solution and the Test solution into the chromatograph, record the chromatograms, and measure the peak responses. Calculate the per centage of any impurity in the portion of Gabapentin taken by the formula:

\[
100\left(\frac{F}{C_1}\right)\left(\frac{C_1}{r_S}\right)
\]

in which \(F\) is the relative response factor of the impurity (relative to gabapentin related compound E) according to Table 1; \(C_1\) is the concentration, in mg per mL, of USP Gabapentin Related Compound E RS in the Standard solution; \(C_1\) is the concentration of Gabapentin, in mg per mL, in the Test solution; \(r_S\) is the peak area for gabapentin related compound E in the Standard solution; the impurities meet the requirements given in Table 1.

LIMIT OF LATE ELUTING IMPURITIES—
Diluent—Dissolve 2.32 g of ammonium phosphate monobasic in 1000 mL of water. Adjust with phosphoric acid to a pH of 2.0.

Buffer solution—Proceed as directed in the Assay.

Mobile phase—Prepare a filtered and degassed mixture of Buffer solution, acetonitrile, and methanol (35:35:30). Make adjustments if necessary (see System Suitability under Chromatography (621)).

Standard solution—Dissolve an accurately weighed quantity of USP Gabapentin Related Compound D RS in a small amount of methanol, and dilute quantitatively, and stepwise if necessary, with Diluent to obtain a solution having a known concentration of about 0.0028 mg per mL.

Test solution—Use the Assay preparation.

Chromatographic system (see Chromatography (621))—The liquid chromatograph is equipped with a 215-nm detector and a 4.6-mm × 25-cm column that contains packing L1. The flow rate is about 1 mL per minute. The column temperature is maintained at 40 °C. Chromatograph the Standard solution, and record the peak responses as directed for Procedure: the column efficiency is not less than 13,600 theoretical plates for the gabapentin related compound D peak; and the relative standard deviation for replicate injections is not more than 7.0%.

### Table 1

<table>
<thead>
<tr>
<th>Compound Name</th>
<th>Relative Retention Time¹ (approximate)</th>
<th>Relative Response Factor²</th>
<th>Limit (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gabapentin related compound E</td>
<td>2.9</td>
<td>1.0</td>
<td>0.10</td>
</tr>
<tr>
<td>Gabapentin related compound A</td>
<td>3.5</td>
<td>5.3</td>
<td>0.1</td>
</tr>
<tr>
<td>Gabapentin related compound B</td>
<td>3.8</td>
<td>0.35</td>
<td>0.06</td>
</tr>
<tr>
<td>Individual unknown impurity</td>
<td>—</td>
<td>0.41</td>
<td>0.10</td>
</tr>
</tbody>
</table>

¹ The relative retention times are calculated based on the retention time of gabapentin. [NOTE—This information is for identification purposes only.]
² The relative response factors are calculated based on the response of gabapentin related compound E due to the low absorptivity of gabapentin at the monitoring wavelength (215 nm).
Procedure—Separately inject equal volumes (about 20 μL) of the Standard solution and the Test solution into the chromatograph, record the chromatograms, and measure the responses for the major peaks. [Note—Disregard all the peaks having relative retention times of 0.35 or less relative to gabapentin related compound D, as these are quantified in the test for Limit of Early Eluting Impurities.] Calculate the percentage of any impurity in the portion of Gabapentin taken by the formula:

\[
100(1/F)(C_i / C_r)(r_i / r_r)
\]

in which \( F \) is the relative response factor of the impurity (relative to gabapentin related compound D) which is 1.0 for gabapentin related compound D and 0.025 for all other impurities, respectively; \( C_i \) is the concentration, in mg per mL, of USP Gabapentin Related Compound D RS in the Standard solution; \( C_r \) is the concentration, in mg per mL, of gabapentin in the Test solution; \( r_i \) is the peak area for any impurity in the Test solution; and \( r_r \) is the peak area for gabapentin related compound D in the Standard solution: not more than 0.10% of any impurity is found, and not more than 0.5% of total impurities (including the impurities quantified in Limit of Early Eluting Impurities) is found.

Assay—

Diluent—Dissolve 2.32 g of monobasic ammonium phosphate in 1000 mL of water. Adjust with phosphoric acid to a pH of 2.0.

Buffer solution—Dilute 1.83 g of sodium per chlorate in 1000 mL of water. Adjust with perchloric acid to a pH of 1.8.

Mobile phase—Prepare a filtered and degassed mixture of Buffer solution and acetonitrile (76:24). Make adjustments if necessary (see System Suitability under Chromatography (621)).

System suitability preparation—Quantitatively dilute a known volume of the Standard preparation with Diluent to obtain a solution having a concentration of about 2.3 mg per mL of gabapentin.

Standard preparation—Dissolve accurately weighed quantity of USP Gabapentin RS in Diluent, and dilute quantitatively, stepwise if necessary, with Diluent to obtain a solution having a known concentration of about 14.0 mg per mL.

Assay preparation—Transfer about 350 mg of Gabapentin, accurately weighed, to a 25-mL volumetric flask, dissolve in and dilute with Diluent to volume, and mix.

Chromatographic system (see Chromatography (621))—The liquid chromatograph is equipped with a 215-nm detector and a 4.6-mm × 25-cm column that contains packing L1. The flow rate is about 1 mL per minute. The column temperature is maintained at 40°. Chromatograph the System suitability preparation, and record the peak responses as directed for Procedure: the column efficiency is not less than 1900 theoretical plates for the gabapentin peak. Chromatograph the Standard preparation, and record the peak responses as directed for Procedure: the relative standard deviation for replicate injections is not more than 2.0% for the gabapentin peak.

Procedure—Separately inject equal volumes (about 20 μL) of the Standard preparation and the Assay preparation into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the per centage of C₉H₁₇NO₂ in the portion of Gabapentin taken by the formula:

\[
100(C_i / C_r)(r_i / r_r)
\]

in which \( C_i \) and \( C_r \) are the concentrations of gabapentin, in mg per mL, in the Standard preparation and the Assay preparation, respectively; and \( r_i \) and \( r_r \) are the peak areas obtained from the Assay preparation and the Standard preparation, respectively.

Gabapentin Capsules

- Gabapentin Capsules contain not less than 90.0 percent and not more than 110.0 per cent of the labeled amount of gabapentin (C₉H₁₇NO₂).

Packaging and storage—Preserve in well-closed containers. Store at controlled room temperature.

USP Reference standards (11)—
- USP Gabapentin RS
- USP Gabapentin Related Compound A RS
- 2-Aza-spiro[4.5]decan-3-one
- C₉H₁₇NO₂ 133.22

Identification—
- A: Infrared Absorption (197K).
- Test specimen—Empty the contents of not fewer than 10 Capsules, and grind to a fine powder. Use an amount of the powder, equivalent to 2 mg of gabapentin, and 200 mg of potassium bromide.
- B: The retention time of the major peak in the chromatogram of the Assay preparation corresponds to that in the chromatogram of the Standard preparation, as obtained in the Assay.

Dissolution (711)—
- Medium: 0.06 N hydrochloric acid (prepared by adding 51 mL of hydrochloric acid to 10 L of water); 900 mL
- Apparatus 2: 50 rpm.
- Time: 20 minutes.

Determine the amount of gabapentin (C₉H₁₇NO₂) dissolved by employing the following method.

Mobile phase—Proceed as directed in the Assay.

Standard stock solution—Dissolve an accurately weighed quantity of USP Gabapentin RS in the Medium to obtain a solution having a known concentration of about 1.1 mg per mL.

Working standard solution—
- FOR CAPSULES LABELED TO CONTAIN 100 MG—Transfer 10.0 mL of the Standard stock solution to a 100-mL volumetric flask, and dilute with Medium to volume.
- FOR CAPSULES LABELED TO CONTAIN 400 MG—Transfer 20.0 mL of the Standard stock solution to a 100-mL volumetric flask, and dilute with Medium to volume.

Test solution—Pass a portion of the solution under test through a suitable 0.45-μm filter.

Chromatographic system (see Chromatography (621))—Proceed as directed in the Assay, except to use the Working standard solution.

Procedure—Separately inject equal volumes (about 100 μL) of the appropriate Working standard solution and the Test solution into the chromatograph, record the chromatograms, and measure the peak responses. Calculate the amount of gabapentin (C₉H₁₇NO₂) dissolved by the formula:

\[
\frac{r_i \times C_i \times 900 \times 100}{r_r \times I}
\]

in which \( r_i \) and \( r_r \) are the peak responses for the Working standard solution and the Test solution, respectively; \( C_i \) is the concentration, in mg per mL, of the Working standard solution; 900 is the volume, in mL, of Medium; 100 is the conversion factor to percentage; and \( I \) is the Capsule label claim, in mg.

Tolerances—Not less than 80% (Q) of the labeled amount of gabapentin (C₉H₁₇NO₂) is dissolved in 20 minutes.