Pioglitazone Hydrochloride

C₁₉H₂₀N₂O₃S·HCl  
2,4-Thiazolidinedione, 5-[4-[2-(5-ethyl-2-pyridinyl)ethoxy]phenyl][methyl]-, monohydrochloride, (±); (±)-5-[4-[2-(5-Ethyl-2-pyridyl)ethoxy]phenyl][methyl]-2,4-thiazolidinedione monohydrochloride [112529-15-4].

DEFINITION

Pioglitazone Hydrochloride contains NLT 98.0% and NMT 102.0% of C₁₉H₂₀N₂O₃S·HCl, calculated on the anhydrous basis.

IDENTIFICATION

A. Infrared Absorption (197K)

B. Identification Tests—General, Chloride (191): Dissolve 25 mg of Pioglitazone Hydrochloride in 0.5 mL of nitric acid, and add 2 mL of dilute nitric acid. It meets the requirements of the test for Chloride.

C. The retention time of the pioglitazone peak of the Sample solution corresponds to that of the Standard solution, as obtained in the Assay.

ASSAY

A. Procedure

Mobile phase: Acetonitrile, 0.1 M ammonium acetate, and glacial acetic acid (25:25:1)

Standard solution: Prepare a 0.5 mg/mL solution of USP Pioglitazone Hydrochloride RS in methanol, and dilute with Mobile phase to obtain a solution containing 50 µg/mL of pioglitazone hydrochloride.

System suitability stock solution: 0.5 mg/mL of USP Pioglitazone Hydrochloride RS and 0.13 mg/mL of benzophenone in methanol

System suitability solution: Dilute System suitability stock solution with Mobile phase to obtain a solution containing 50 µg/mL of pioglitazone hydrochloride and 13 µg/mL of benzophenone.

Sample solution: Prepare a 0.5 mg/mL solution of pioglitazone hydrochloride in methanol, and dilute with Mobile phase to obtain a solution containing 50 µg/mL of pioglitazone hydrochloride.

Chromatographic system

(See Chromatography (621), System Suitability.)

Mode: LC
Detector: UV 269 nm
Column: 4.6-mm x 15-cm; 5-µm packing L1
Column temperature: 25 ± 2°C
Flow rate: 0.7 mL/min
[NOTE—Adjust the flow rate so that the retention time of the pioglitazone peak is about 7 min.]
Injection size: 20 µL

System suitability

Samples: System suitability solution and Standard solution
[NOTE—The approximate relative retention times for pioglitazone and benzophenone are 1.0 and 2.6, respectively.]

Suitability requirements

Tailing factor: NMT 1.5 for pioglitazone and benzophenone, System suitability solution

Resolution: NLT 15 between pioglitazone and benzophenone, System suitability solution

Relative standard deviation: NMT 2.0% for six replicate injections, Standard solution

Analysis

Samples: Standard solution and Sample solution

Calculate the percentage of C₁₉H₂₀N₂O₃S·HCl in the portion of Pioglitazone Hydrochloride taken:

\[ \text{Result} = \left( \frac{r_u}{r_S} \right) \times \left( \frac{C_S}{C_U} \right) \times 100 \]

\( r_u \) = peak response from the Sample solution
\( r_S \) = peak response from the Standard solution
\( C_S \) = concentration of USP Pioglitazone Hydrochloride RS in the Standard solution (µg/mL)
\( C_U \) = concentration of Pioglitazone Hydrochloride in the Sample solution (µg/mL)

Acceptance criteria: 98.0%–102.0% on the anhydrous basis

IMPURITIES

Inorganic Impurities

Residue on Ignition (281): NMT 0.1%

Heavy Metals

Sodium sulfide solution: 5 g of sodium sulfide in 10 mL of water and 30 mL of glycerin
Magnesium nitrate solution: 100 mg/mL of magnesium nitrate in alcohol

Standard solution: Place 10 mL of Magnesium nitrate solution in a platinum or porcelain crucible. Ignite the alcohol to burn. Cool, add 1 mL of sulfuric acid, heat carefully, and ignite at 550 ± 50°C. Cool and add 3 mL of hydrobromic acid. Proceed as directed from this point under Sample solution, adding 1.0 mL of Standard Lead Solution (see Heavy Metals (231), Special Reagents) before adding water to make 50 mL.

Sample solution: Place 1.0 g of pioglitazone hydrochloride in a platinum or porcelain crucible. Mix with 10 mL of Magnesium nitrate solution. Ignite the alcohol to burn, and carbonize by gradual heating. Cool, add 1 mL of sulfuric acid, heat carefully, and incinerate by ignition at 550 ± 50°C. If carbonized substances remain, moisten with a small amount of sulfuric acid, and incinerate by ignition. Cool, dissolve the residue in 3 mL of hydrobromic acid, and evaporate on a water bath to dryness. Wet the residue with 3 drops of hydrochloric acid, add 10 mL of water and dissolve by warming. Add 1 drop of phenolphthalein TS, and add ammonia TS dropwise until a pale red color develops. Add 2 mL of 1 N acetic acid, filter if necessary, wash with 10 mL of water, transfer the filtrate and washings to a Nessler tube, and add water to make 50 mL.

Analysis: Add 1 drop of Sodium sulfide solution to each of the tubes containing the Standard solution and Sample solution. Mix thoroughly and allow to stand for 5 min. Compare the colors of both solutions by viewing the tubes downward or transversely against a white background. The Sample solution has no more color than the Standard solution.

Acceptance criteria: NMT 10 ppm

Organic Impurities

A. Procedure

Mobile phase and System suitability stock solution: Proceed as directed in the Assay.

System suitability solution: Dilute the System suitability stock solution with Mobile phase to obtain a solution containing 25 µg/mL of pioglitazone hydrochloride and 6.5 µg/mL of benzophenone.

Sample solution: 0.2 mg/mL of pioglitazone hydrochloride dissolved in 20% of the final volume with methanol, then diluted with Mobile phase to final volume

Standard solution: 1 µg/mL of pioglitazone hydrochloride prepared by diluting the Sample solution with Mobile phase

quantity, in mg, of pindolol (C₁₄H₂₀N₂O₂) in the portion of Tablets taken by the formula:

\[ 100C(t_0 / t_s) \]

in which C is the concentration, in mg per mL, of USP Pindolol RS in the Standard preparation; and \( t_0 \) and \( t_s \) are the pindolol peak responses obtained from the Assay preparation and the Standard preparation, respectively.
Chromatographic system
(See Chromatography (621), System Suitability.)
Mode: LC
Detector: UV 269 nm
Column: 4.6-mm × 15-cm; 5-μm packing L1
Column temperature: 25 ± 2.5°
Flow rate: 0.7 mL/min
[NOTE—Adjust the flow rate so that the retention time of the pioglitazone peak is about 7 min.]
Injection size: 40 μL
Run time: At least four times the retention time of pioglitazone
System suitability
Samples: System suitability solution and Standard solution
Suitability requirements
Tailing factor: NMT 1.5 for pioglitazone and benzophenone, System suitability solution
Resolution: NLT 15 between pioglitazone and benzophenone, System suitability solution
Relative standard deviation: NMT 3.0%, Standard solution
Analysis
Samples: Standard solution and Sample solution
Calculate the percentage of each impurity in the portion of Pioglitazone Hydrochloride taken:

\[ \text{Result} = \left( \frac{r_U}{r_S} \right) \times D \times 100 \]

- \( r_U \) = peak response of each individual impurity from the Sample solution
- \( r_S \) = peak response of pioglitazone from the Standard solution
- \( D \) = dilution factor used to prepare the Standard solution, 0.005

Acceptance criteria
Individual impurities: See Impurity Table 1.
Total impurities: NMT 0.5%

### Impurity Table 1

<table>
<thead>
<tr>
<th>Name</th>
<th>Relative Retention Time</th>
<th>Acceptance Criteria, NMT (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydroxypioglitazone</td>
<td>0.7</td>
<td>0.15</td>
</tr>
<tr>
<td>Pioglitazone</td>
<td>1.0</td>
<td>—</td>
</tr>
<tr>
<td>Didehydropioglitazone</td>
<td>1.4</td>
<td>0.15</td>
</tr>
<tr>
<td>N-Alkylpioglitazone</td>
<td>3.0</td>
<td>0.15</td>
</tr>
<tr>
<td>Any other individual impurity</td>
<td>—</td>
<td>0.10</td>
</tr>
</tbody>
</table>

- \( * \)-(5)-4-[2-(5-Ethylpyridin-2-yl)ethoxy]benzyl)-S-hydroxythiazolidine-2,4-dione.
- \( * \)-(5)-5-[4-(2-(5-Ethylpyridin-2-yl)ethoxy]benzylidene]thiazolidine-2,4-dione.

SPECIFIC TESTS
- WATER DETERMINATION, Method lc (921): NMT 0.5%

ADDITIONAL REQUIREMENTS
- PACKAGING AND STORAGE: Preserve in well-closed containers, and store at room temperature.
- USP REFERENCE STANDARDS (11)
  - USP Pioglitazone Hydrochloride RS

### Pioglitazone Tablets

DEFINITION
Pioglitazone Tablets contain an amount of pioglitazone hydrochloride (C_{19}H_{20}N_{2}O_{3}S·HCl) equivalent to NLT 95.0% and NMT 105.0% of the labeled amount of pioglitazone (C_{19}H_{20}N_{2}O_{3}S).

IDENTIFICATION
- A. The retention time of the pioglitazone peak of the Sample solution corresponds to that of the Standard solution, as obtained in the Assay.
- B. ULTRAVIOLET ABSORPTION

Sample solution: Dissolve a quantity of finely powdered Tablets in 0.1 N hydrochloric acid to obtain a solution containing 25 μg/mL of pioglitazone. [NOTE—Vigorous shaking and filtration may be needed.]

Acceptance criteria: The UV absorption spectrum exhibits a maximum between 267 and 271 nm.

ASSAY
- PROCEDURE

Mobile phase: Acetonitrile, 0.1 M ammonium acetate, and glacial acetic acid (25:25:1)

Standard solution: Prepare 0.5 mg/mL solution of USP Pioglitazone Hydrochloride RS in methanol, and dilute with Mobile phase to obtain a solution containing 50 μg/mL of pioglitazone hydrochloride.

System suitability stock solution: 0.5 mg/mL of USP Pioglitazone Hydrochloride RS and 0.13 mg/mL of benzophenone in methanol.

System suitability solution: Dilute the System suitability stock solution with Mobile phase to obtain a solution containing 50 μg/mL of pioglitazone hydrochloride and 13 μg/mL of benzophenone.

Sample solution: Weigh and finely powder NLT 20 Tablets. Transfer an accurately weighed portion of the powder, equivalent to about 23 mg of pioglitazone, to a glass-stoppered flask, and add 50 mL of methanol. Disperse the particles by sonication for about 2 min, then centrifuge. Dilute a portion of the supernatant with Mobile phase to obtain a solution having a nominal concentration of 45 μg/mL of pioglitazone.

Chromatographic system
(See Chromatography (621), System Suitability.)
Mode: LC
Detector: UV 269 nm
Column: 4.6-mm × 15-cm; 5-μm packing L1
Column temperature: 25 ± 2.5°
Flow rate: 0.7 mL/min
[NOTE—Adjust the flow rate so that the retention time of the pioglitazone peak is about 7 min.]
Injection size: 20 μL
System suitability
Samples: Standard solution and System suitability solution
[NOTE—The approximate relative retention times for pioglitazone and benzophenone are 1.0 and 2.6, respectively.]
Suitability requirements
Tailing factor: NMT 1.5 for pioglitazone and benzophenone, System suitability solution
Resolution: NLT 15 between pioglitazone and benzophenone, System suitability solution
Relative standard deviation: NMT 2.0% for six replicate injections, Standard solution
Analysis
Samples: Standard solution and Sample solution
Calculate the percentage of the labeled amount of C_{19}H_{20}N_{2}O_{3}S in the portion of Tablets taken:

\[ \text{Result} = \left( \frac{r_U}{r_S} \right) \times \left( \frac{C_S}{C_U} \right) \times \left( \frac{M_2}{M_1} \right) \times 100 \]

- \( r_U \) = peak response from the Sample solution
- \( r_S \) = peak response from the Standard solution
- \( C_S \) = concentration of USP Pioglitazone Hydrochloride RS in the Standard solution (μg/mL)
- \( C_U \) = nominal concentration of pioglitazone in the Sample solution (μg/mL)
- \( M_1 \) = molecular weight of pioglitazone, 356.44
- \( M_2 \) = molecular weight of pioglitazone hydrochloride, 392.90