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Pioglitazone and Glimepiride Tablets

DEFINITION

Pioglitazone and Glimepiride Tablets contain an amount of pioglitazone hydrochloride ($C_{19}H_{20}N_2O_3S \cdot HCl$) equivalent to NLT 90.0% and NMT 110.0% of the labeled amount of pioglitazone ($C_{19}H_{20}N_2O_3S$), and NLT 90.0% and NMT 110.0% of the labeled amount of glimepiride ($C_{24}H_{34}N_4O_5S$).

IDENTIFICATION

• **A. Ultraviolet Absorption**

Sample: Transfer 1 Tablet to a suitable container, and add 0.1 N hydrochloric acid to obtain a final concentration of about 0.1 mg/mL of glimepiride. Shake until the Tablet disintegrates. Pass a 2-mL portion of the resulting suspension through a suitable filter of 0.45-µm pore size. Use the filtrate for the identification of pioglitazone, and use the filter for the identification of glimepiride.

Pioglitazone

Sample solution: Dilute a portion of the filtrate obtained in the *Sample* with 0.1 N hydrochloric acid to obtain a solution containing about 0.03 mg/mL of pioglitazone.

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

Glimepiride

Sample solution: Wash the filter, as obtained in the *Sample*, with 100 mL of 0.1 N hydrochloric acid, and discard the filtrate. Wash the filter with 20 mL of methanol, and use the filtrate.

Acceptance criteria: The UV absorption spectrum exhibits a maximum between 227 and 231 nm.

• **B.** The retention times of the pioglitazone and glimepiride peaks of the *Sample solution* correspond to those of the *Standard solution,* as obtained in the *Assay*.

ASSAY

• **Procedure**

Buffer: 6.9 g/L of monobasic sodium phosphate in water, adjusted with diluted phosphoric acid to a pH of 4.0

Mobile phase: Acetonitrile and *Buffer* (1:1)

Diluent: Acetonitrile and 0.1 N hydrochloric acid (9:1)

Standard stock solution: 0.66 mg/mL of USP Pioglitazone Hydrochloride RS and 0.08 mg/mL of USP Glimepiride RS in *Diluent*

Standard solution: 66 µg/mL of pioglitazone hydrochloride and 8 µg/mL of glimepiride in *Mobile phase* from the *Standard stock solution*

Resolution stock solution: Dilute 1.0 mL of ethyl benzoate with *Mobile phase* to 100 mL. Further dilute 1.0 mL of the resulting solution with *Mobile phase* to 100 mL.

System suitability solution: Transfer 5.0 mL of the *Standard stock solution* and 5.0 mL of the *Resolution stock solution* to a 50-mL volumetric flask, and dilute with *Mobile phase* to volume.

Sample stock solution: Transfer 20 Tablets to a suitable container. Add 200.0 mL of *Diluent*, and shake vigorously for at least 20 min. If disintegration is not complete, sonicate until the Tablets are completely disintegrated, and then shake for an additional 10 min. Pass through a suitable filter of 0.2-µm pore size, discarding the first few mL of filtrate. Further dilute 5.0 mL of the filtrate with *Diluent* to 50.0 mL.

Sample solution: Transfer 10.0 mL of the *Sample stock solution* to a 50-mL volumetric flask, and dilute with *Mobile phase* to volume to obtain a solution with the nominal concentrations listed in *Table 1*.

Table 1

Labeled Amounts of Pioglitazone and Glimepiride (mg/Tablet)	Nominal Concentrations in the *Sample solution*	
	Pioglitazone (µg/mL)	Glimepiride (µg/mL)
30 and 2	60	4
30 and 4	60	8

Chromatographic system

(See *Chromatography ⟨621⟩, System Suitability*.)

Mode: LC

Detector: UV 228 nm

Column: 4.6-mm × 5-cm; 3-µm packing L1

Column temperature: 25 ± 5°

Flow rate: 0.8 mL/min. [NOTE—The flow rate may be adjusted to achieve the retention time of the pioglitazone peak of about 2.3 min.]

Injection volume: 20 µL

System suitability

Samples: *Standard solution* and *System suitability solution*

[NOTE—See *Table 2* for the approximate relative retention times.]

Table 2

Name	Relative Retention Time
Pioglitazone	1.0
Ethyl benzoate	1.7
Glimepiride	2.3

Suitability requirements

Resolution: NLT 4 between pioglitazone and ethyl benzoate; NLT 3 between ethyl benzoate and glimepiride, *System suitability solution*

Relative standard deviation: NMT 1.0% for the pioglitazone peak; NMT 1.0% for the glimepiride peak, *Standard solution*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of pioglitazone ($C_{19}H_{20}N_2O_3S$) in the portion of Tablets taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times (M_{r1}/M_{r2}) \times 100$$

r_U = peak response of pioglitazone from the *Sample solution*

r_S = peak response of pioglitazone 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_{r1} = molecular weight of pioglitazone, 356.44

M_{r2} = molecular weight of pioglitazone hydrochloride, 392.90

Calculate the percentage of the labeled amount of glimepiride ($C_{24}H_{34}N_4O_5S$) in the portion of Tablets taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times 100$$

r_U = peak response of glimepiride from the *Sample solution*

r_S = peak response of glimepiride from the *Standard solution*

C_S = concentration of USP Glimepiride RS in the *Standard solution* (µg/mL)

C_U = nominal concentration of glimepiride in the *Sample solution* (µg/mL)

Acceptance criteria: 90.0%–110.0% for each of the labeled amounts of pioglitazone and glimepiride

PERFORMANCE TESTS

• **Dissolution** ⟨711⟩

Test 1

Pioglitazone

Medium: Hydrochloric acid buffer pH 2.0 (see *Reagents, Indicators, and Solutions—Buffer Solutions*); 900 mL

Apparatus 2: 75 rpm

Time: 15 min

Mobile phase and **Chromatographic system:** Proceed as directed in the *Assay.*

Standard stock solution: 0.37 mg/mL of USP Pioglitazone Hydrochloride RS dissolved first in methanol using 20% of the final volume, and then diluted with *Medium* to volume

Standard solution: Transfer 10.0 mL of the *Standard stock solution* to a 100-mL volumetric flask, and dilute with *Medium* to volume.

Sample solution: Pass a portion of the solution under test through a suitable filter of 0.45-µm pore size.

System suitability

Sample: *Standard solution*

Suitability requirements

Tailing factor: NMT 2.0

Relative standard deviation: NMT 2.0%

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of pioglitazone ($C_{19}H_{20}N_2O_3S$) dissolved:

$$\text{Result} = (r_U/r_S) \times (C_S/L) \times V \times (M_{r1}/M_{r2}) \times 100$$

r_U = peak response of pioglitazone from the *Sample solution*

r_S = peak response of pioglitazone from the *Standard solution*

C_S = concentration of USP Pioglitazone Hydrochloride RS in the *Standard solution* (mg/mL)

L = labeled amount of pioglitazone (mg/Tablet)

V = volume of *Medium,* 900 mL

M_{r1} = molecular weight of pioglitazone, 356.44

M_{r2} = molecular weight of pioglitazone hydrochloride, 392.90

Tolerances: NLT 80% (*Q*) of the labeled amount of pioglitazone ($C_{19}H_{20}N_2O_3S$) is dissolved.

Glimepiride

Medium: pH 6.8 sodium phosphate buffer containing 0.2% of sodium dodecyl sulfate (6.9 g/L of monobasic sodium phosphate, 0.896 g/L of sodium hydroxide, and 2 g/L of sodium dodecyl sulfate in water, adjusted with 1 N sodium hydroxide to a pH of 6.8); 900 mL

Apparatus 2: 75 rpm

Time: 15 min

Mobile phase and **Chromatographic system:** Proceed as directed in the *Assay.* The flow rate may be adjusted to achieve the retention time of the glimepiride peak of about 5.4 min.

Standard stock solution: 0.22 mg/mL of USP Glimepiride RS in acetonitrile

Standard solution: *L*/900 mg/mL of USP Glimepiride RS in *Medium*, where *L* is the labeled amount of glimepiride, in mg/Tablet, from the *Standard stock solution*

Sample solution: Pass a portion of the solution under test through a suitable filter of 0.45-µm pore size.

System suitability

Sample: *Standard solution*

Suitability requirements

Tailing factor: NMT 2.0

Relative standard deviation: NMT 2.0%

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of glimepiride ($C_{24}H_{34}N_4O_5S$) dissolved:

$$\text{Result} = (r_U/r_S) \times (C_S/L) \times V \times 100$$

r_U = peak response of glimepiride from the *Sample solution*

r_S = peak response of glimepiride from the *Standard solution*

C_S = concentration of USP Glimepiride RS in the *Standard solution* (mg/mL)

L = labeled amount of glimepiride (mg/Tablet)

V = volume of *Medium*, 900 mL

Tolerances: NLT 80% (*Q*) of the labeled amount of glimepiride ($C_{24}H_{34}N_4O_5S$) is dissolved.

Test 2: If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 2*.

Pioglitazone

Medium: Hydrochloric acid buffer pH 2.0 (see *Reagents, Indicators, and Solutions—Buffer Solutions*); 900 mL, deaerated

Apparatus 2: 75 rpm

Time: 30 min

Buffer: 0.02 M sodium phosphate buffer pH 2.5 (2.75 g/L of monobasic sodium phosphate in water, adjusted with phosphoric acid to a pH of 2.5)

Solution A: Acetonitrile and *Buffer* (28:72)

Solution B: Acetonitrile and *Buffer* (70:30)

Mobile phase: See *Table 3*.

Table 3

Time (min)	Solution A (%)	Solution B (%)
0	100	0
4.0	0	100
7.0	0	100

Return to original conditions and re-equilibrate the system.

Standard stock solution: 0.2 mg/mL of USP Pioglitazone Hydrochloride RS dissolved first in alcohol using 20% of the final volume, and then diluted with *Medium* to volume

Standard solution: Transfer 5.0 mL of the *Standard stock solution* to a 25-mL volumetric flask, and dilute with *Medium* to volume.

Sample solution: Pass a portion of the solution under test through a suitable filter of 0.45-µm pore size.

Chromatographic system

(See *Chromatography ⟨621⟩, System Suitability*.)

Mode: LC

Detector: UV 225 nm for pioglitazone (0–4.0 min) and UV 230 nm for glimepiride (4.0–7.0 min)

Column: 4.6-mm × 15-cm; 3.5-µm packing L1

Column temperature: 30°

Flow rate: 1.5 mL/min

Injection volume: 20 µL

System suitability

Sample: *Standard solution*

Suitability requirements

Tailing factor: NMT 2.0

Relative standard deviation: NMT 2.0%

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of pioglitazone ($C_{19}H_{20}N_2O_3S$) dissolved:

$$\text{Result} = (r_U/r_S) \times (C_S/L) \times V \times (M_{r1}/M_{r2}) \times 100$$

r_U = peak response of pioglitazone from the *Sample solution*

r_S = peak response of pioglitazone from the *Standard solution*

C_S = concentration of USP Pioglitazone Hydrochloride RS in the *Standard solution* (mg/mL)

L = labeled amount of pioglitazone (mg/Tablet)

V = volume of *Medium*, 900 mL

M_{r1} = molecular weight of pioglitazone, 356.44

M_{r2} = molecular weight of pioglitazone hydrochloride, 392.90

Tolerances: NLT 80% (Q) of the labeled amount of pioglitazone ($C_{19}H_{20}N_2O_3S$) is dissolved.

Glimepiride

Medium: pH 6.8 sodium phosphate buffer containing 0.2% of sodium dodecyl sulfate (6.9 g/L of monobasic sodium phosphate, 0.896 g/L of sodium hydroxide, and 2 g/L of sodium dodecyl sulfate in water, adjusted with 1 N sodium hydroxide to a pH of 6.8); 900 mL

Apparatus 2: 75 rpm

Time: 15 min

Mobile phase and **Chromatographic system:** Proceed as directed in *Dissolution Test 2*, *Pioglitazone*.

Standard stock solution: 0.2 mg/mL of USP Glimepiride RS in alcohol

Standard solution: L/900 mg/mL of USP Glimepiride RS in *Medium*, where L is the labeled amount of glimepiride, in mg/Tablet, from the *Standard stock solution*

Sample solution: Pass a portion of the solution under test through a suitable filter of 0.45-µm pore size.

System suitability

Sample: *Standard solution*

Suitability requirements

Tailing factor: NMT 2.0

Relative standard deviation: NMT 2.0%

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of glimepiride ($C_{24}H_{34}N_4O_5S$) dissolved:

$$\text{Result} = (r_U/r_S) \times (C_S/L) \times V \times 100$$

r_U = peak response of glimepiride from the *Sample solution*

r_S = peak response of glimepiride from the *Standard solution*

C_S = concentration of USP Glimepiride RS in the *Standard solution* (mg/mL)

L = labeled amount of glimepiride (mg/Tablet)

V = volume of *Medium*, 900 mL

Tolerances: NLT 80% (Q) of the labeled amount of glimepiride ($C_{24}H_{34}N_4O_5S$) is dissolved.

• **Uniformity of Dosage Units ⟨905⟩:** Meet the requirements for *Content Uniformity* for pioglitazone and glimepiride

IMPURITIES

• **Organic Impurities: Pioglitazone**

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

Diluent: Acetonitrile and 0.1 N hydrochloric acid (9:1)

Standard stock solution: 0.2 mg/mL of USP Pioglitazone Hydrochloride RS in *Diluent*

Standard solution: 2 µg/mL of USP Pioglitazone Hydrochloride RS in *Mobile phase* from the *Standard stock solution*

Resolution stock solution: Dilute 1.0 mL of ethyl benzoate to 100.0 mL with acetonitrile. Further dilute 1.0 mL of the resulting solution with acetonitrile to 100.0 mL.

System suitability solution: Transfer 2.0 mL of the *Resolution stock solution* into a 100-mL volumetric flask. Add 1.0 mL of the *Standard stock solution,* and dilute with *Mobile phase* to volume.

Sample stock solution: Transfer 10 Tablets to an appropriate volumetric flask such that the nominal glimepiride concentration is 0.4 mg/mL. Add *Diluent* to approximately 80% of the total volume. Shake vigorously for at least 20 min, and dilute with *Diluent* to volume. Pass through a suitable filter of 0.2-µm pore size, discarding the first few mL of filtrate.

Sample solution: Transfer a suitable volume of the *Sample stock solution* to a 25-mL volumetric flask, and dilute with *Mobile phase* to volume to obtain a solution containing 240 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 ± 5°

Flow rate: 0.8 mL/min. [NOTE—The flow rate may be adjusted to achieve the retention time of the pioglitazone peak of about 7 min.]

Injection volume: 40 µL

Run time: At least 4 times the retention time of the pioglitazone peak

System suitability

Samples: *Standard solution* and *System suitability solution*

[NOTE—Elution order is the pioglitazone peak followed by ethyl benzoate.]

Suitability requirements

Resolution: NLT 10 between pioglitazone and ethyl benzoate, *System suitability solution*

Tailing factor: NMT 1.5 for the pioglitazone peak, *System suitability solution*

Relative standard deviation: NMT 5.0%, *Standard solution*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of each pioglitazone related impurity in the portion of Tablets taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times (M_{r1}/M_{r2}) \times 100$$

r_U = peak response of each individual impurity from the *Sample solution*

r_S = peak response of pioglitazone 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_{r1} = molecular weight of pioglitazone, 356.44

M_{r2} = molecular weight of pioglitazone hydrochloride, 392.90

Acceptance criteria

Any individual pioglitazone related impurity: NMT 0.2%

Total pioglitazone related impurities: NMT 0.6%

[NOTE—Disregard the peak due to glimepiride, which elutes at about 16.5 min.]

Change to read:

• **ORGANIC IMPURITIES: GLIMEPIRIDE**

Buffer: 0.007 M sodium phosphate, pH 1.6 (0.97 g/L of monobasic sodium phosphate in water, adjusted with dilute phosphoric acid to a pH of 1.6)

Diluent: Acetonitrile and 0.1 N hydrochloric acid (9:1)

Solution A: Acetonitrile and *Buffer* (52:48)

Solution B: Acetonitrile and *Buffer* (70:30)

Mobile phase: See *Table ▲4▲* (ERR 1-Oct-2018) .

Table ▲4▲ (ERR 1-Oct-2018)

Time (min)	Solution A (%)	Solution B (%)
0	100	0
15	100	0
60	0	100
60.1	100	0
70	100	0

Standard stock solution: 0.2 mg/mL of USP Glimepiride RS in *Diluent*

Standard solution: 2 µg/mL of USP Glimepiride RS in *Solution A* from the *Standard stock solution*

Resolution stock solution: Dilute 1.0 mL of ethyl benzoate with acetonitrile to 100.0 mL. Further dilute 1.0 mL of the resulting solution with acetonitrile to 100.0 mL.

System suitability solution: Transfer 2 mL of the *Resolution stock solution* into a 100-mL volumetric flask, add 1.0 mL of the *Standard stock solution,* and dilute with *Solution A* to volume.

Sample stock solution: Transfer 10 Tablets to an appropriate volumetric flask such that the nominal glimepiride concentration is 0.4 mg/mL. Add *Diluent* to approximately 80% of the total volume. Shake vigorously for at least 20 min, and dilute with *Diluent* to volume. Pass through a suitable filter of 0.2-µm pore size, discarding the first few mL of filtrate.

Sample solution: Equivalent to 0.2 mg/mL glimepiride in *Solution A* from the *Sample stock solution*

Chromatographic system

(See *Chromatography ⟨621⟩, System Suitability*.)

Mode: LC

Detector: UV 228 nm

Column: 4.6-mm × 25-cm; 5-µm packing L1

Column temperature: 25 ± 5°

Flow rate: 1.0 mL/min. [NOTE—The flow rate may be adjusted to achieve the retention time of the glimepiride peak of about 25 min.]

Injection volume: 40 µL

System suitability

Samples: *Standard solution* and *System suitability solution*

[NOTE—Elution order is ethyl benzoate followed by glimepiride.]

Suitability requirements

Resolution: NLT 10 between ethyl benzoate and glimepiride, *System suitability solution*

Tailing factor: NMT 1.5 for glimepiride, *System suitability solution*

Relative standard deviation: NMT 5.0%, *Standard solution*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of each glimepiride related impurity in the portion of Tablets taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times (1/F) \times 100$$

r_U = peak response of each individual impurity from the *Sample solution*

r_S = peak response of glimepiride from the *Standard solution*

C_S = concentration of USP Glimepiride RS in the *Standard solution* (mg/mL)

C_U = nominal concentration of glimepiride in the *Sample solution* (mg/mL)

F = relative response factor for each impurity (see *Table ▲5▲* (ERR 1-Oct-2018))

Acceptance criteria: See *Table ▲5▲* (ERR 1-Oct-2018) . [NOTE—Disregard the peaks due to inactive ingredients and to pioglitazone that elute before the glimepiride sulfonamide peak.]

Table ▲5▲ (ERR 1-Oct-2018)

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Glimepiride sulfonamide (glimepiride related compound B)[a]	0.2	1.39	1.5
Glimepiride	1.0	1.0	—
Any other glimepiride related individual impurity	—	1.0	0.2
Total glimepiride related impurities	—	—	2.5

[a] [*p*-[2-(3-Ethyl-4-methyl-2-oxo-3-pyrroline-1-carboxamido)ethyl]phenyl] sulfonamide.

ADDITIONAL REQUIREMENTS

- **PACKAGING AND STORAGE:** Preserve in tight containers, and store at controlled room temperature.
- **LABELING:** When more than one dissolution test is given, the labeling states the *Dissolution Test* used only if *Test 1* is not used.
- **USP REFERENCE STANDARDS** ⟨11⟩
  USP Glimepiride RS
  USP Pioglitazone Hydrochloride RS

Auxiliary Information - Please check for your question in the FAQs before contacting USP.

Topic/Question	Contact	Expert Committee
PIOGLITAZONE AND GLIMEPIRIDE TABLETS	Documentary Standards Support	SM32020 Small Molecules 3
REFERENCE STANDARD SUPPORT	RS Technical Services RSTECH@usp.org	SM32020 Small Molecules 3

Chromatographic Database Information: Chromatographic Database

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