Pioglitazone and Metformin Hydrochloride Tablets

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Reason for Revision	Compliance

In accordance with the Rules and Procedures of the 2015-2020 Council of Experts, the Chemical Medicines Monographs 3 Expert Committee has revised the Pioglitazone and Metformin Hydrochloride Tablets monograph. The purpose for the revision is to include an option of using UV spectra of the pioglitazone and metformin peaks in the *Sample solution* and the *Standard solution* as obtained in the *Assay* to meet the Acceptance criteria under the *Identification Test* A, and to modify the wavelength ranges for absorption maxima. This will address the comments that the excipient matrix in some products may interfere with the *Ultraviolet Absorption <197U>* test.

The Pioglitazone and Metformin Hydrochloride Tablets Revision Bulletin supersedes the currently official monograph. The Revision Bulletin will be incorporated in the *USP 40–NF 35*.

Should you have any questions, please contact Elena Gonikberg, Ph.D., Principal Scientific Liaison, (301–816-8251 or eg@usp.org).

Pioglitazone and Metformin Hydrochloride Tablets

DEFINITION

Pioglitazone and Metformin Hydrochloride Tablets contain an amount of pioglitazone hydrochloride ($C_{19}H_{20}N_2O_3S \cdot HCl$) equivalent to NLT 95.0% and NMT 105.0% of the labeled amount of pioglitazone ($C_{19}H_{20}N_2O_3S$), and NLT 95.0% and NMT 105.0% of the labeled amount of metformin hydrochloride ($C_4H_{11}N_5 \cdot HCl$).

IDENTIFICATION

Change to read:

- **A. ULTRAVIOLET ABSORPTION** ⟨197U⟩

  •[NOTE—The UV spectra of the major peaks of the *Sample solution* and the *Standard solution* as obtained in the *Assay* may also be used to meet the *Acceptance criteria.*]• (RB 1-Jun-2016)

  Pioglitazone

  Sample solution: Transfer a quantity of finely powdered Tablets to a suitable container, and add water to obtain a final concentration of about 0.03 mg/mL of pioglitazone. Sonicate for about 30 s. Pass through a 5-mL portion of the resulting suspension using a suitable filter of 0.45-µm pore size, then wash the filter with 10 mL of water, and discard the filtrate. Wash the filter with 5 mL of 0.1 N hydrochloric acid, and use the filtrate.

  Acceptance criteria: The UV absorption spectrum exhibits a maximum between •265• (RB 1-Jun-2016) and 271 nm.

  Metformin hydrochloride

  Sample solution: Transfer a quantity of finely powdered Tablets to a suitable container, and add a suitable quantity of water, based on the labeled amount of metformin hydrochloride in the sample, to obtain a final concentration of about 0.4 mg/mL of metformin hydrochloride. Sonicate for about 30 s, and pass through a suitable filter of 0.45-µm pore size, discarding the first few mL of filtrate. Dilute a portion of the filtrate with water to obtain a solution containing about 8 µg/mL of metformin hydrochloride.

  Acceptance criteria: The UV absorption spectrum exhibits a maximum between 230 and •235• (RB 1-Jun-2016) nm.

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

ASSAY

Change to read:

- **PROCEDURE**

  Mobile phase: 7.2 g/L of sodium dodecyl sulfate in a mixture of 0.05 M monobasic ammonium phosphate and acetonitrile (1:1)

  Diluent: Methanol and 0.1 N hydrochloric acid (1:1)

  System suitability stock solution: 0.5 mg/mL of *p*-methoxyacetophenone and 0.4 mg/mL of butylparaben in *Diluent*

  Pioglitazone standard stock solution: 0.84 mg/mL of USP Pioglitazone Hydrochloride RS in *Diluent*

  Mixed standard stock solution: 2.5 mg/mL of USP Metformin Hydrochloride RS and 0.084 mg/mL of USP Pioglitazone Hydrochloride RS in 0.1 N hydrochloric acid from the *Pioglitazone standard stock solution*

  System suitability solution: Transfer 10.0 mL of the *Mixed standard stock solution* and 5.0 mL of the *System suitability stock solution* to a 50-mL volumetric flask, and dilute with 0.1 N hydrochloric acid to volume.

  Standard solution: 16.8 µg/mL of USP Pioglitazone Hydrochloride RS and 0.5 mg/mL of USP Metformin Hydrochloride RS in 0.1 N hydrochloric acid from the *Mixed standard stock solution*

  Sample stock solution: Weigh and finely powder NLT 10 Tablets. Transfer an amount of powdered Tablets, equivalent to about 15 mg of pioglitazone, to a 200-mL volumetric flask. Add 120 mL of 0.1 N hydrochloric acid, shake for about 30 min, and then sonicate for about 5 min. Dilute with 0.1 N hydrochloric acid to volume, and mix well. Pass through a suitable filter of 0.45-µm pore size, discarding the first few mL of filtrate.

  Sample solution: Transfer a suitable volume of the *Sample stock solution* (see *Table 1*) to a 50-mL volumetric flask, and dilute with 0.1 N hydrochloric acid to volume.

Table 1

Labeled Amount of Pioglitazone and Metformin Hydrochloride (mg/Tablet)	Volume of Sample Stock Solution Used to Prepare the Sample Solution (mL)	Nominal Concentrations in the Sample Solution	
		Pioglitazone (µg/mL)	Metformin Hydrochloride (mg/mL)
15 and 500	10	15	0.5
15 and 850	5	7.5	0.425

  Chromatographic system

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

  Mode: LC

  Detector: UV 255 nm for metformin and *p*-methoxyacetophenone; UV 225 nm for pioglitazone and butylparaben. •If this procedure is used for *Identification A*, use a diode-array detector set at 200–400 nm.• (RB 1-Jun-2016)

  Column: 6.0-mm × 15-cm; 5-µm packing L7

  Column temperature: 25 ± 5°

  Flow rate: 1 mL/min. [NOTE—The flow rate may be adjusted to achieve the retention time of the metformin peak of about 5 min.]

  Injection volume: 10 µL

  System suitability

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

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

Table 2

Name	Relative Retention Time
Metformin	1.0
p-Methoxyacetophenone	1.2
Pioglitazone	1.8
Butylparaben	2.1

  Suitability requirements

  Resolution: NLT 2.5 between metformin and *p*-methoxyacetophenone; NLT 2.5 between pioglitazone and butylparaben, *System suitability solution*

  Relative standard deviation: NMT 1.0% for the metformin peak; NMT 1.0% for pioglitazone 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 metformin hydrochloride ($C_4H_{11}N_5 \cdot HCl$) in the portion of Tablets taken:

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

r_U = peak response of metformin from the *Sample solution*
r_S = peak response of metformin from the *Standard solution*
C_S = concentration of USP Metformin Hydrochloride RS in the *Standard solution* (mg/mL)
C_U = nominal concentration of metformin hydrochloride in the *Sample solution* (mg/mL)

Acceptance criteria: 95.0%–105.0% for each of the labeled amounts of pioglitazone and metformin hydrochloride

PERFORMANCE TESTS

• **Dissolution** ⟨**711**⟩

Test 1
Medium: pH 2.5 McIlvaine buffer (could be prepared by adjusting 0.1 M citric acid with 0.2 M dibasic sodium phosphate to a pH of 2.5); 900 mL
Apparatus 2: 50 rpm
Time: 30 min
Diluent and **Mobile phase:** Proceed as directed in the *Assay*.
Pioglitazone standard stock solution: 0.37 mg/mL of USP Pioglitazone Hydrochloride RS in *Diluent*
Standard solution: 0.0185 mg/mL of USP Pioglitazone Hydrochloride RS from the *Pioglitazone standard stock solution* and (*L*/900) mg/mL of USP Metformin Hydrochloride RS in *Medium*, where *L* is the label claim, in mg/Tablet, of metformin hydrochloride
Sample solution: Pass a portion of the solution under test through a suitable filter of 0.45-µm pore size.
Chromatographic system: Proceed as directed in the *Assay*, except use an *Injection volume* of 5 µL.
System suitability
Sample: *Standard solution*
Suitability requirements
Tailing factor: NMT 2.5 for the metformin peak; NMT 2.0 for the pioglitazone peak
Relative standard deviation: NMT 2.0% for the metformin peak; NMT 2.0% for the pioglitazone peak

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 = label claim 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

Calculate the percentage of the labeled amount of metformin hydrochloride ($C_4H_{11}N_5 \cdot HCl$) dissolved:

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

r_U = peak response of metformin hydrochloride from the *Sample solution*
r_S = peak response of metformin hydrochloride from the *Standard solution*
C_S = concentration of USP Metformin Hydrochloride RS in the *Standard solution* (mg/mL)
L = label claim of metformin hydrochloride (mg/Tablet)
V = volume of *Medium*, 900 mL

Tolerances: NLT 80% (*Q*) of the labeled amount of pioglitazone ($C_{19}H_{20}N_2O_3S$) is dissolved; NLT 80% (*Q*) of the labeled amount of metformin hydrochloride ($C_4H_{11}N_5 \cdot HCl$) is dissolved.

Test 2: If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 2*.
Medium: pH 2.5 McIlvaine buffer (could be prepared by adjusting 0.1 M citric acid with 0.2 M dibasic sodium phosphate to a pH of 2.5); 900 mL
Apparatus 2: 50 rpm
Time: 45 min
Solution A: 1.4 g/L of dibasic sodium phosphate anhydrous and 1.4 g/L of sodium dodecyl sulfate in water
Solution B: Phosphoric acid and water (50:50)
Mobile phase: Acetonitrile and *Solution A* (34:66). Adjust with *Solution B* to a pH of 7.1.
Diluent A: Acetonitrile and *Medium* (50:50)
Diluent B: Acetonitrile and water (70:30)
Pioglitazone standard stock solution: 0.019 mg/mL of USP Pioglitazone Hydrochloride RS in *Diluent B*. Sonicate as needed to dissolve.
Metformin standard stock solution: 0.92 mg/mL of USP Metformin Hydrochloride RS in *Medium*. Sonicate as needed to dissolve.
Standard solution: 0.003 mg/mL of USP Pioglitazone Hydrochloride RS from the *Pioglitazone standard stock solution* and 0.11 mg/mL of USP Metformin Hydrochloride RS in *Diluent A*
Sample solution: Pass a portion of the solution under test through a suitable filter and dilute with *Diluent A* to a metformin concentration that is similar to the *Standard solution*.
Chromatographic system
(See *Chromatography* ⟨621⟩*, System Suitability*.)

Mode: LC
Detector: UV 225 nm
Column: 4.6-mm × 15-cm; 5-µm packing L1
Temperatures
Autosampler: 5°
Column: 40°
Flow rate: 1 mL/min
Injection volume: 15 µL
System suitability
Sample: *Standard solution*
Suitability requirements
Tailing factor: 0.8–2.0 for the metformin peak; 0.8–2.0 for the pioglitazone peak
Relative standard deviation: NMT 2.0% for the metformin peak; NMT 2.5% for the pioglitazone peak
Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the percentage of the labeled amount of pioglitazone ($C_{19}H_{20}N_2O_3S$) dissolved:

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

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 = label claim of pioglitazone (mg/Tablet)
V = volume of *Medium,* 900 mL
D = dilution factor of the *Sample solution*
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 metformin hydrochloride ($C_4H_{11}N_5 \cdot HCl$) dissolved:

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

r_U = peak response of metformin hydrochloride from the *Sample solution*
r_S = peak response of metformin hydrochloride from the *Standard solution*
C_S = concentration of USP Metformin Hydrochloride RS in the *Standard solution* (mg/mL)
L = label claim of metformin hydrochloride (mg/Tablet)
V = volume of *Medium*, 900 mL
D = dilution factor of the *Sample solution*

Tolerances: NLT 80% (Q) of the labeled amount of pioglitazone ($C_{19}H_{20}N_2O_3S$) is dissolved; NLT 80% (Q) of the labeled amount of metformin hydrochloride ($C_4H_{11}N_5 \cdot HCl$) is dissolved.

- **Uniformity of Dosage Units** ⟨**905**⟩**,** *Content Uniformity***:** Meet the requirements for pioglitazone and metformin hydrochloride

IMPURITIES

- **Organic Impurities: Pioglitazone**

Mobile phase: Acetonitrile, 0.1 M ammonium acetate, and glacial acetic acid (25:25:1)
Diluent: Methanol and 0.1 N hydrochloric acid (1:1)
Standard stock solution: 0.2 mg/mL of USP Pioglitazone Hydrochloride RS, dissolved first in methanol using 20% of the final volume, then diluted with *Mobile phase* to volume
System suitability solution: Prepare a solution containing 0.3 mg/mL of benzophenone in methanol. Transfer 1.0 mL of this solution to a 50-mL volumetric flask, add 5.0 mL of the *Standard stock solution*, and dilute with *Mobile phase* to volume. This solution contains 20 µg/mL of USP Pioglitazone Hydrochloride RS and 6 µg/mL of benzophenone.
Standard solution: 1 µg/mL of USP Pioglitazone Hydrochloride RS in *Mobile phase* from the *Standard stock solution*
Sample solution: Weigh and finely powder 10 Tablets. Transfer an amount of powdered Tablets, equivalent to about 18 mg of pioglitazone, to a 100-mL volumetric flask, and add 50 mL of *Diluent*. Shake for 30 min, and dilute with *Mobile phase* to volume. Pass through a suitable filter of 0.45-µm pore size, discarding the first few mL of filtrate.
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: *System suitability solution* and *Standard solution*
[NOTE—Elution order is the pioglitazone peak followed by benzophenone.]
Suitability requirements
Resolution: NLT 10 between pioglitazone and benzophenone, *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 peaks due to metformin and its impurities that elute before 4.5 min, corresponding to the relative retention time of the pioglitazone peak of about 0.64.]

- **Organic Impurities: Metformin**

Solution A: 1.74 g of sodium 1-pentanesulfonate and 1.15 g of monobasic ammonium phosphate in 1000 mL of water

Solution B: Acetonitrile and water (7:3)
Mobile phase: See *Table 3*.

Table 3

Time (min)	Solution A (%)	Solution B (%)
0	100	0
15	70	30
15.1	0	100
25	0	100
25.1	100	0
35	100	0

System suitability solution: 5 µg/mL of USP Metformin Hydrochloride RS and 2 µg/mL of melamine in water
Standard solution: 5 µg/mL of USP Metformin Hydrochloride RS in water
Sample solution: Accurately weigh 10 Tablets, and finely powder. Transfer an amount of powdered Tablets, equivalent to about 100 mg of metformin hydrochloride, to a 100-mL volumetric flask, and add 50 mL of water. Shake for 30 min. Dilute with water to volume, and pass through a suitable filter of 0.45-µm pore size, discarding the first few mL of filtrate.
Chromatographic system
(See *Chromatography* ⟨621⟩, *System Suitability*.)
Mode: LC
Detector: UV 215 nm
Column: 4.6-mm × 15-cm; 5-µm packing L62
Column temperature: 25 ± 5°
Flow rate: 1.0 mL/min. [NOTE—The flow rate may be adjusted to achieve the retention time of the metformin peak of about 8 min.]
Run time: 15 min
Injection volume: 20 µL
System suitability
Samples: *System suitability solution* and *Standard solution*
[NOTE—The relative retention times for melamine and metformin are about 0.9 and 1.0, respectively.]
Suitability requirements
Resolution: NLT 4 between melamine and metformin hydrochloride, *System suitability solution*
Tailing factor: NMT 1.5 for the metformin hydrochloride peak, *System suitability solution*
Relative standard deviation: NMT 5.0%, *Standard solution*
Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the percentage of each metformin hydrochloride related impurity in the portion of Tablets taken:

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

r_U = peak response of each individual impurity from the *Sample solution*
r_S = peak response of metformin hydrochloride from the *Standard solution*
C_S = concentration of USP Metformin Hydrochloride RS in the *Standard solution* (µg/mL)
C_U = nominal concentration of metformin hydrochloride in the *Sample solution* (µg/mL)

Acceptance criteria
Any individual impurity: NMT 0.1%
Total impurities: NMT 0.5%

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 Metformin Hydrochloride RS
  USP Pioglitazone Hydrochloride RS