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Glyburide and Metformin Hydrochloride Tablets

DEFINITION

Glyburide and Metformin Hydrochloride Tablets contain NLT 90.0% and NMT 110.0% of the labeled amounts of glyburide ($C_{23}H_{28}ClN_3O_5S$) and metformin hydrochloride ($C_4H_{11}N_5 \cdot HCl$).

IDENTIFICATION

• **A. Glyburide:** The retention time of the glyburide peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay* for *Glyburide*.

• **B. Metformin Hydrochloride:** The retention time of the major peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay* for *Metformin Hydrochloride*.

ASSAY

• **Glyburide**

Buffer: 28.8 g/L of monobasic ammonium phosphate

Mobile phase: Acetonitrile and *Buffer* (40:60). Adjust with 1 N sodium hydroxide to a pH of 5.3.

Diluent: Acetonitrile and water (50:50)

Standard stock solution: 0.25 mg/mL of USP Glyburide RS prepared as follows. Transfer a weighed amount of USP Glyburide RS to a suitable volumetric flask. Dissolve first in the acetonitrile, using 50% of the final volume, and then dilute with water to volume.

Standard solution: 0.025 mg/mL of USP Glyburide RS in *Diluent*, from the *Standard stock solution*

System suitability solution 1: Prepare a solution containing 0.025 mg/mL of USP Glyburide Related Compound A RS in *Diluent*. Transfer 50 µL of this solution to a 50-mL volumetric flask, and dilute with *Standard solution* to volume.

System suitability solution 2: 5.0 mg/mL of USP Metformin Hydrochloride RS in *System suitability solution 1*

Sample solution: Dissolve NLT 5 Tablets in *Diluent* by stirring with a magnetic stirring bar for at least 1 h. Dilute to obtain a solution containing 0.025 mg/mL of glyburide, based on the label claim. Centrifuge a portion of this solution at 3000 rpm for 10 min and use the clear supernatant. [Note—Retain a portion of this solution for the *Assay* for *Metformin Hydrochloride*.]

Chromatographic system

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

Mode: LC

Detector: UV 230 nm

Column: 4.6-mm × 15-cm; 5-µm packing L7

Column temperature: 40°

Flow rate: 1.2 mL/min

Injection volume: 100 µL

Run time: 1.25 times the retention time of glyburide

System suitability

Sample: *System suitability solution 2*

[Note—The relative retention time for glyburide related compound A is about 0.30 with respect to glyburide.]

Suitability requirements

Relative standard deviation: NMT 1.5% for the glyburide peak; NMT 10% for the glyburide related compound A peak

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of glyburide ($C_{23}H_{28}ClN_3O_5S$) in the portion of Tablets taken:

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

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

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

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

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

Acceptance criteria: 90.0%–110.0% of the labeled amount of glyburide

- **Metformin Hydrochloride**

Buffer: Transfer 1.0 g each of sodium heptanesulfonate and sodium chloride to a 2000-mL volumetric flask. Add 1800 mL of water, and adjust with 0.06 M phosphoric acid to a pH of 3.85. Dilute with water to volume.

Mobile phase: Acetonitrile and *Buffer* (10:90)

[Note—To improve the separation, the composition of acetonitrile and *Buffer* may be changed to 5:95, if necessary.]

Diluent: Acetonitrile and water (1:40)

Standard solution: 0.25 mg/mL of USP Metformin Hydrochloride RS in *Diluent*. [Note—Sonicate to achieve complete dissolution, if necessary.]

System suitability stock solution: 25 µg/mL each of USP Metformin Related Compound B RS and USP Metformin Related Compound C RS in *Diluent*

System suitability solution: Transfer 0.5 mL of the *System suitability stock solution* to a 50-mL volumetric flask, and dilute with *Standard solution* to volume.

Sample solution: Dilute with water a portion of the retained *Sample solution* from the *Assay* for *Glyburide* to obtain 0.25 mg/mL of metformin hydrochloride based on the label claim.

Chromatographic system

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

Mode: LC

Detector: UV 218 nm

Column: 3.9-mm × 30-cm; 10-µm packing L1

Column temperature: 30°

Flow rate: 1 mL/min

Injection volume: 5 µL

System suitability

Sample: *System suitability solution*

[Note—The relative retention times for metformin related compound B, metformin, and metformin related compound C are about 0.86, 1.0, and 2.1–2.3, respectively. Metformin related compound C can have a variable retention time. The composition of acetonitrile and *Buffer* in *Mobile phase* may be changed to 5:95, if it elutes at a relative retention time of less than 2.1.]

Suitability requirements

Resolution: NLT 1.5 between metformin related compound B and metformin

Tailing factor: 0.8–2.0 for the metformin peak

Relative standard deviation: NMT 1.5% for the metformin peak; NMT 10% each for the metformin related compound B and metformin related compound C peaks

Analysis

Samples: *Standard solution* and *Sample solution*

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: 90.0%–110.0% of the labeled amount of metformin hydrochloride

PERFORMANCE TESTS

- **Dissolution ⟨711⟩**

Test 1

Glyburide

Medium: 0.05 M boric acid and 0.05 M potassium chloride solution. Prepare by dissolving 3.09 g of boric acid and 3.73 g of potassium chloride in 250 mL of water, adjust with 1 N sodium hydroxide to a pH of 9.5, and dilute with water to 1 L; 500 mL.

Apparatus 2: 75 rpm

Time: 30 min

Standard solution: 0.1 mg/mL of USP Glyburide RS prepared as follows. Transfer a weighed amount of USP Glyburide RS to a suitable volumetric flask, dissolve first in acetonitrile, using 20% of the final volume, then dilute with *Medium* to volume. Dilute further with *Medium* to obtain a solution having a glyburide concentration, in mg/mL, of (*L*/500), where *L* is the label claim of glyburide in mg/Tablet.

Sample solution: Sample per *Dissolution* ⟨711⟩. Pass a portion of the solution under test through a polypropylene filter of 0.45-µm pore size or a glass fiber filter of 1-µm pore size.

Buffer: 28.8 g/L of monobasic ammonium phosphate in water

Mobile phase: Acetonitrile and *Buffer* (1:1). Adjust with 1 N sodium hydroxide to a pH of 5.3.

Chromatographic system

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

Mode: LC

Detector: UV 230 nm

Column: 4.6-mm × 15-cm; 5-µm packing L7

Column temperature: 30°

Flow rate: 1.5 mL/min

Injection volume: 200 µL

System suitability

Sample: *Standard solution*

Suitability requirements

Tailing factor: 0.8–2.0

Relative standard deviation: NMT 2%

Analysis

Samples: *Standard solution* and *Sample solution*

Determine the percentage of the labeled amount of glyburide ($C_{23}H_{28}ClN_3O_5S$) dissolved:

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

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

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

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

L = label claim of glyburide (mg/Tablet)

V = volume of *Medium*, 500 mL

Tolerances: NLT 85% (*Q*) of the labeled amount of glyburide is dissolved.

Metformin hydrochloride

Medium: 0.05 M phosphate buffer, pH 6.8. Prepare by dissolving 6.8 g of monobasic potassium phosphate in 1000 mL of water, and adjust with 0.2 N sodium hydroxide to a pH of 6.8 ± 0.1; 1000 mL.

Apparatus 2: 50 rpm

Time: 30 min

Standard solution: Dissolve a quantity of USP Metformin Hydrochloride RS in *Medium*, to obtain a solution having a metformin hydrochloride concentration, in mg/mL, of (*L*/1000), where *L* is the label claim of metformin hydrochloride in mg/Tablet. Dilute further, if necessary, with *Medium*.

Sample solution: Sample per *Dissolution* ⟨711⟩. Pass a portion of the solution under test through a polypropylene filter of 0.45-µm pore size or a glass fiber filter of 1-µm pore size. Dilute with *Medium*, if necessary, to a concentration similar to that of the *Standard solution*.

Instrumental conditions

(See *Ultraviolet-Visible Spectroscopy* ⟨857⟩.)

Mode: UV-Vis

Analytical wavelength: 232 nm

Analysis

Samples: *Standard solution* and *Sample solution*

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

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

A_U = absorbance of the *Sample solution*

A_S = absorbance of the *Standard solution*

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

L = label claim (mg/Tablet)

V = volume of *Medium*, 1000 mL

D = dilution factor for the *Sample solution*

Tolerances: NLT 85% (Q) of the labeled amount of metformin hydrochloride is dissolved.

Test 2

Glyburide

Medium: 0.05 M boric acid and 0.05 M potassium chloride solution. Prepare by dissolving 3.09 g of boric acid and 3.73 g of potassium chloride in 250 mL of water, adjust with 1 N sodium hydroxide to a pH of 9.5, and dilute with water to 1 L; 500 mL.

Apparatus 2: 75 rpm

Time: 30 min

Solution A: Dissolve 0.288 g of sodium lauryl sulfate in 700 mL water.

Mobile phase: Acetonitrile, *Solution A*, and triethylamine (300:700:2). Adjust with phosphoric acid to a pH of 7.2.

Standard stock solution: 0.1 mg/mL of USP Glyburide RS prepared in acetonitrile

Standard solution: Dilute *Standard stock solution* with *Medium* to obtain a solution having a glyburide concentration, in mg/mL, of (L/500), where L is the label claim of glyburide in mg/Tablet.

Sample solution: Sample per *Dissolution* ⟨711⟩. Pass a portion of the solution under test through a membrane filter of 0.45-µm pore size.

Chromatographic system

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

Mode: LC

Detector: UV 220 nm

Column: 4.6-mm × 15-cm; 5-µm packing L7

Column temperature: 40°

Flow rate: 2 mL/min

Injection volume

For Tablets labeled to contain 5 mg/500 mg and 2.5 mg/500 mg: 20 µL

For Tablets labeled to contain 1.25 mg/250 mg: 50 µL

Run time: 8 min

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*

Determine the percentage of the labeled amount of glyburide ($C_{23}H_{28}ClN_3O_5S$) dissolved:

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

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

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

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

L = label claim of glyburide (mg/Tablet)

V = volume of *Medium*, 500 mL

Tolerances: NLT 80% (*Q*) of the labeled amount of glyburide is dissolved.

Metformin hydrochloride

Medium: 0.05 M phosphate buffer, pH 6.8. Prepare by dissolving 6.8 g of monobasic potassium phosphate in 1000 mL of water, and adjust with 0.2 N sodium hydroxide to a pH of 6.8 ± 0.1; 1000 mL.

Apparatus 2: 50 rpm

Time: 30 min

Solution A: Dissolve 0.288 g of sodium lauryl sulfate in 700 mL of water.

Mobile phase: Acetonitrile, *Solution A*, and triethylamine (300:700:2). Adjust with phosphoric acid to a pH of 7.2.

Standard solution

For Tablets labeled to contain 5 mg/500 mg and 2.5 mg/500 mg: 0.5 mg/mL of USP Metformin Hydrochloride RS in *Medium*. Sonicate before final dilution.

For Tablets labeled to contain 1.25 mg/250 mg: 0.25 mg/mL of USP Metformin Hydrochloride RS in *Medium*. Sonicate before final dilution.

Sample solution: Sample per *Dissolution ⟨711⟩*. Pass a portion of the solution under test through a membrane filter of 0.45-µm pore size.

Chromatographic system

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

Mode: LC

Detector: UV 254 nm

Column: 4.6-mm × 15-cm; 5-µm packing L7

Column temperature: 40°

Flow rate: 2 mL/min

Injection volume

For Tablets labeled to contain 5 mg/500 mg and 2.5 mg/500 mg: 20 µL

For Tablets labeled to contain 1.25 mg/250 mg: 50 µL

Run time: 8 min

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*

Determine 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 the *Sample solution*

r_S = peak response of the *Standard solution*

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

L = label claim (mg/Tablet)

V = volume of *Medium*, 1000 mL

Tolerances: NLT 85% (*Q*) of the labeled amount of metformin hydrochloride is dissolved.

• **Uniformity of Dosage Units ⟨905⟩:** Meet the requirements for *Weight Variation* for metformin hydrochloride and for *Content Uniformity* for glyburide

IMPURITIES

• **Glyburide**

Buffer, Mobile phase, Diluent, Sample solution, Chromatographic system, and **System suitability:** Proceed as directed in the *Assay* for *Glyburide*.

Standard solution: Dilute 1.0 mL of the *Standard solution* from the *Assay* for *Glyburide* with *Diluent* to 100 mL.

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of each glyburide 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 glyburide impurity from the *Sample solution*

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

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

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

F = relative response factor, 1.2 for glyburide related compound A, 1.0 for all other impurities

Acceptance criteria

[NOTE—Disregard any peak less than 0.05%, and disregard any peak observed in the blank.]

Glyburide related compound A: NMT 1.0%

Any other individual impurities: NMT 0.2%

Total impurities: NMT 0.50%, excluding glyburide related compound A

- **METFORMIN HYDROCHLORIDE**

Buffer, Mobile phase, Sample solution, Chromatographic system, and **System suitability:** Proceed as directed in the *Assay* for *Metformin Hydrochloride*.

Analysis

Sample: *Sample solution*

Calculate the percentage of each metformin impurity in the portion of Tablets taken:

$$\text{Result} = (r_U/r_T) \times 100$$

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

r_T = sum of all the peak responses from the *Sample solution*

Acceptance criteria

[NOTE—Disregard any peak less than 0.05%, and disregard any peak observed in the blank.]

Individual metformin impurities: NMT 0.1%

Total impurities: NMT 0.5 %

ADDITIONAL REQUIREMENTS

- **PACKAGING AND STORAGE:** Preserve in tight, light-resistant 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.

Change to read:

- **USP REFERENCE STANDARDS** ⟨11⟩

USP Glyburide RS

USP Glyburide Related Compound A RS

4-[2-(5-Chloro-2-methoxybenzamido)ethyl]benzenesulfonamide.

$C_{16}H_{17}ClN_2O_4S$ ▲368.83▲ (ERR 1-Apr-2021)

USP Metformin Hydrochloride RS

USP Metformin Related Compound B RS

1-Methylbiguanide hydrochloride.

$C_3H_9N_5 \cdot HCl$ 151.60

USP Metformin Related Compound C RS

Dimethylmelamine, or *N,N*-dimethyl-[1,3,5]triazine-2,4,6-triamine.

$C_5H_{10}N_6$ 154.17

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

Topic/Question	Contact	Expert Committee
GLYBURIDE AND METFORMIN HYDROCHLORIDE TABLETS	Documentary Standards Support	SM32020 Small Molecules 3

Chromatographic Database Information: Chromatographic Database

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