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Glipizide and Metformin Hydrochloride Tablets

DEFINITION

Glipizide and Metformin Hydrochloride Tablets contain NLT 90.0% and NMT 110.0% of the labeled amounts of glipizide ($C_{21}H_{27}N_5O_4S$) and metformin hydrochloride ($C_4H_{11}N_5 \cdot HCl$).

IDENTIFICATION

Change to read:

• **A.** ▲**Spectroscopic Identification Tests** ⟨197⟩, *Infrared Spectroscopy*: **197A**▲ (CN 1-May-2020)

Sample: Transfer NLT 10 Tablets to a suitable container, add 10 mL of methanol, and shake to remove any Tablet coating. Drain the methanol, add 20 mL of water, and stir until the Tablets dissolve (1 h). Transfer the solution to a separatory funnel, and extract twice with 10-mL portions of chloroform, shaking for approximately 5 min. Transfer the lower organic layer into a beaker containing 3 to 4 g of anhydrous magnesium sulfate. Repeat the extraction of the solution in the separatory funnel two more times, each time using 20-mL portions of chloroform. Swirl the mixture in the beaker for 1 min. Filter, and collect the filtrate. Evaporate the solvent under vacuum, and dry the residue under vacuum for 4 h at 105°. Mound the residue onto a diamond cell.

Acceptance criteria: The IR spectrum exhibits maxima only at the same wavelengths as a similarly obtained spectrum of USP Glipizide RS.

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

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

ASSAY

• **Glipizide**

Solution A: 2.6 g/L of dibasic ammonium phosphate in water. Adjust with ammonium hydroxide to a pH of 8.0.

Solution B: Acetonitrile, water, and *Solution A* (1:14:5)

Solution C: Acetonitrile, water, and *Solution A* (2:1:1)

Diluent: Acetonitrile and water (60:40)

Standard stock solution: Transfer a weighed quantity of USP Glipizide RS to a suitable low-actinic volumetric flask. Dissolve first in acetonitrile, using 60% of the final volume, by sonicating for 20 min, then dilute with water to volume to obtain a solution having a concentration of 0.1 mg/mL of glipizide. [Note—The solution is stable for 2 weeks when stored at 5° and protected from light.]

Standard solution: Transfer 25.0 mL of *Standard stock solution* to a 200-mL low-actinic volumetric flask. Add 75 mL of *Diluent*, and dilute with water to volume to obtain a solution having a known glipizide concentration of 0.0125 mg/mL. [Note—The solution is stable for 2 weeks when stored at 5° and protected from light.]

System suitability solution: Transfer approximately 5 mg of USP Glipizide Related Compound A RS to a 500-mL volumetric flask, and fill halfway with acetonitrile. Sonicate for 30 min to dissolve, and dilute with acetonitrile to volume. Transfer 1 mL of this solution to a 50-mL low-actinic volumetric flask, and dilute with *Standard solution* to volume.

Sample solution: Transfer NLT 5 Tablets to a suitable volumetric flask, and fill halfway with *Diluent*. Sonicate for 30 min, and shake vigorously for another 30 min to dissolve. Dilute with water to volume, and mix to obtain a solution with a final glipizide concentration of 0.0125 mg/mL. Pass a portion of this solution through a nylon or PVDF filter of 0.2-µm pore size, and use the filtrate. [Note—The solution is stable for 2 weeks when stored at 5° and protected from light.]

Mobile phase: See the gradient table below.

Time (min)	Solution B (%)	Solution C (%)
0	100	0

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Time (min)	Solution B (%)	Solution C (%)
3	100	0
18	0	100
20	0	100
22	100	0
30	100	0

Chromatographic system

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

Mode: LC

Detector: UV 223 nm

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

Flow rate: 1 mL/min

Injection size: 50 µL

System suitability

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

[NOTE—The relative retention times for glipizide related compound A and glipizide are 0.92 and 1.0, respectively.]

Suitability requirements

Resolution: Greater than 1.2 between glipizide related compound A and glipizide, *System suitability solution*

Relative standard deviation: Less than 2.0%, *Standard solution*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of $C_{21}H_{27}N_5O_4S$ in the portion of Tablets taken:

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

r_U = peak response from the *Sample solution*

r_S = peak response from the *Standard solution*

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

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

Acceptance criteria: 90.0%–110.0%

- **METFORMIN HYDROCHLORIDE**

Solution A: 9.41 g/L of sodium 1-hexanesulfonate in water, and adjust with trifluoroacetic acid to a pH of 2.0 (50 mM hexanesulfonic acid solution)

Solution B: Acetonitrile and water (40:60)

Mobile phase: *Solution A*, *Solution B*, and water (3:2:5)

Diluent pH 2.0: Acetonitrile, *Solution A*, and water (7:30:63)

Standard solution: 0.1 mg/mL of USP Metformin Hydrochloride RS in *Diluent pH 2.0*

System suitability solution: 5 µg/mL of USP Metformin Related Compound A RS in water. Pipet 0.5 mL of this solution into a 50-mL volumetric flask, and dilute with *Standard solution* to volume.

Sample solution: Dilute a portion of the *Sample solution*, obtained as directed in the *Assay* for *Glipizide*, with *Diluent pH 2.0*, to obtain a solution having a concentration of 0.1 mg/mL of metformin hydrochloride.

Chromatographic system

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

Mode: LC

Detector: UV 218 nm

Column: 4.6-mm × 15-cm; 3.5-µm packing L11

Flow rate: 1 mL/min

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Injection size: 25 µL

System suitability

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

[NOTE—The relative retention times for metformin related compound A and metformin are 0.26 and 1.0, respectively.]

Suitability requirements

Resolution: NLT 3.0 between metformin related compound A and metformin, *System suitability solution*

Relative standard deviation: Less than 2.0%, determined from the metformin peak, *Standard solution*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of $C_4H_{11}N_5 \cdot HCl$ in each Tablet taken:

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

r_U = peak response from the *Sample solution*

r_S = peak response 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%

PERFORMANCE TESTS

• **DISSOLUTION ⟨711⟩**

Test 1

Medium: 0.05 M phosphate buffer, pH 6.8 ± 0.05. (Dissolve 12.96 g of monobasic potassium phosphate and 1.66 g of sodium hydroxide in approximately 400 mL of water, and dilute with water to 2000 mL. Adjust the pH, if necessary, with diluted sodium hydroxide); 1000 mL. [NOTE—Tight control of the pH is critical.]

Apparatus 2: 50 rpm

Time: 45 min for glipizide, and 30 min for metformin hydrochloride.

Determination of glipizide: Determine the amount of glipizide ($C_{21}H_{27}N_5O_4S$) dissolved as follows.

Solution A: Dissolve approximately 3.4 g of monobasic potassium phosphate in approximately 800 mL of water. Adjust with 10 N sodium hydroxide solution to a pH of 6.0 ± 0.1. Dilute with water to 1000 mL.

Mobile phase: Methanol and *Solution A* (13:12)

Standard stock solution: Transfer 50 mg of USP Glipizide RS to a 1000-mL low-actinic volumetric flask, and dissolve in 100 mL of methanol. Dilute with *Medium* to volume, and sonicate for 5 min. [NOTE—This solution is stable for 7 days at 5° when protected from light.]

Standard solution: Dilute the *Standard stock solution* with *Medium* to obtain a solution containing (L/1000) mg/mL, with L being the glipizide Tablet label claim, in mg.

Sample solution: After the specified time, withdraw 10 mL of the solution under test. Pass the solution through a suitable PVDF filter of 0.45-µm pore size or a glass fiber filter of 1.0-µm pore size, discarding the first mL.

Chromatographic system

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

Mode: LC

Detector: UV 220 nm

Column: 4.6-mm × 15-cm; 5-µm packing L1

Flow rate: 1 mL/min

Injection size: 50 µL

System suitability

Sample: *Standard solution*

Suitability requirements

Relative standard deviation: NMT 2.0%

Analysis

Samples: *Standard solution* and *Sample solution*

Record the chromatograms running for 8 min and measure the peak response for glipizide.

Calculate the percentage of $C_{21}H_{27}N_5O_4S$ dissolved:

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

r_U = peak response from the *Sample solution*

C_S = concentration of glipizide in the *Standard solution* (mg/mL)

V = volume of *Medium*, 1000 mL

r_S = peak response from the *Standard solution*

L = label claim for glipizide (mg/Tablet)

Determination of metformin hydrochloride: Determine the amount of metformin hydrochloride dissolved by employing UV absorption at the wavelength of maximum absorbance at 233 nm on portions of the *Sample solution*, suitably diluted with *Medium*, if necessary, in comparison with a *Standard solution* having a known concentration of USP Metformin Hydrochloride RS in the same *Medium*. Calculate the amount of $C_4H_{11}N_5 \cdot HCl$ dissolved:

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

A_U = absorbance from the *Sample solution*

C_S = concentration of the *Standard solution* (mg/mL)

V = volume of *Medium*, 1000 mL

A_S = absorbance from the *Standard solution*

L = label claim for metformin hydrochloride (mg/Tablet)

Tolerances: NLT 80% (Q) of the labeled amount of $C_{21}H_{27}N_5O_4S$ is dissolved in 45 min. NLT 80% (Q) of the labeled amount of $C_4H_{11}N_5 \cdot HCl$ is dissolved in 30 min.

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

Medium: 0.05 M phosphate buffer, pH 6.8; 1000 mL

Apparatus 2: 50 rpm

Time: 60 min for both metformin hydrochloride and glipizide

pH 6.0 buffer solution: 4.3 g/L of octanesulfonic acid sodium salt and 6.9 g/L of monobasic monohydrate sodium phosphate in water, adjusted with diluted sodium hydroxide to a pH of 6.00 ± 0.05

Glipizide standard stock solution: 0.05 mg/mL of USP Glipizide RS in methanol

Standard solution: Transfer a quantity of USP Metformin Hydrochloride RS to a volumetric flask, add a suitable aliquot of *Glipizide standard stock solution*, and dilute with *Medium* to obtain a final concentration of (L/1000) mg/mL, where L is the Tablet label claim for both metformin hydrochloride and glipizide, in mg.

Sample solution: Pass a portion of the solution under test through a suitable polyethersulfone filter of 0.45-µm pore size, discarding the first few mL.

Mobile phase: Methanol and *pH 6.0 buffer solution* (1:1)

Chromatographic system

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

Mode: LC

Detector: UV 260 nm

Sample compartment chiller: 4°

Column: 4.6-mm × 25-cm; packing L1

Flow rate: 1.0 mL/min

Injection size: 20 µL

System suitability

Sample: *Standard solution*

Suitability requirements

Resolution: NLT 2 between the glipizide and metformin hydrochloride peaks

Relative standard deviation: NMT 2.0% for both glipizide and metformin hydrochloride

Analysis: Calculate the percentages of $C_{21}H_{27}N_5O_4S$ and $C_4H_{11}N_5 \cdot HCl$ dissolved:

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

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r_U = peak response for glipizide or metformin hydrochloride from the *Sample solution*

r_S = peak response for glipizide or metformin hydrochloride from the *Standard solution*

C_S = concentration of glipizide or metformin hydrochloride in the *Standard solution* (mg/mL)

L = label claim for glipizide or metformin hydrochloride (mg/Tablet)

V = volume of *Medium*, 1000 mL

Tolerances: NLT 80% (Q) of the labeled amounts of $C_{21}H_{27}N_5O_4S$ and $C_4H_{11}N_5 \cdot HCl$ is dissolved.

• **Uniformity of Dosage Units ⟨905⟩:** Meet the requirements

IMPURITIES

Organic Impurities

• **Procedure 1: Glipizide**

Solution A, Solution B, Solution C, Sample solution, and **Chromatographic system:** Prepare as directed in the *Assay* for *Glipizide*.

Analysis

Sample: *Sample solution*

Calculate the percentage of glipizide related compound A (approximate relative retention time 0.92) and other individual impurities in the portion of Tablets taken:

$$\text{Result} = (r_U/r_T) \times (1/F) \times 100$$

r_U = peak response of each impurity

r_T = sum of all the peak responses

F = relative response factor for each impurity equal to 1.4 for glipizide related compound A and 1.0 for all other peaks

Acceptance criteria

Glipizide related compound A: NMT 2.0%

Individual impurities: NMT 0.5% of any other individual glipizide related impurity (eluting after approximately 8 min)

Total impurities: NMT 1.0%, excluding glipizide related compound A. [Note—Disregard the broad peak due to metformin that elutes before 8 min. Disregard any peak observed in the blank, and disregard any peak less than 0.05%.]

• **Procedure 2: Metformin Hydrochloride**

Solution A, Solution B, Mobile phase, Sample solution, and **Chromatographic system:** Prepare as directed in the *Assay* for *Metformin Hydrochloride*.

Analysis

Sample: *Sample solution*

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

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

r_U = peak response for each impurity

r_T = sum of all the peak responses

Acceptance criteria

Individual impurities: NMT 0.1%

Total impurities: NMT 0.5%

[Note—Disregard any peak less than 0.05%. Disregard any peak observed in the blank.]

ADDITIONAL REQUIREMENTS

• **Packaging and Storage:** Preserve in well-closed 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 Glipizide RS

USP Glipizide Related Compound A RS

N-{2-[(4-Aminosulfonyl)phenyl]ethyl}-5-methyl-pyrazinecarboxamide.

$C_{14}H_{16}N_4O_3S$ 320.37

USP Metformin Hydrochloride RS

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USP Metformin Related Compound A RS
1-Cyanoguanidine.

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

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

Chromatographic Database Information: Chromatographic Database

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