Glipizide and Metformin Hydrochloride Tablets

» Glipizide and Metformin Hydrochloride Tablets contain not less than 90.0 percent and not more than 110.0 percent of the labeled amounts of glipizide ($C_{21}H_{27}N_5O_4S$) and metformin hydrochloride ($C_4H_{11}N_5 \cdot HCl$).

Packaging and storage—Preserve in well-closed containers, and store at controlled room temperature.

Add the following:

•**Labeling—**When more than one *Dissolution* test is given, the labeling states the *Dissolution test* used only if *Test 1* is not used.• (RB 1-Dec-2009)

USP Reference standards ⟨11⟩**—***USP Glipizide RS*. *USP Glipizide Related Compound A RS*. *USP Metformin Hydrochloride RS*. *USP Metformin Related Compound A RS*.

Identification—

A: GLIPIZIDE—

Infrared Absorption ⟨197A⟩—Prepare the test specimen as follows. Transfer not fewer than 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 (about 1 hour). Transfer the solution to a separatory funnel, and extract twice with 10-mL portions of chloroform, shaking for approximately 5 minutes. 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 about 1 minute. Filter, and collect the filtrate. Evaporate the solvent under vacuum, and dry the residue under vacuum for 4 hours at 105°. Mound the residue onto a diamond cell: the IR spectrum so obtained exhibits maxima only at the same wavelengths as a similarly obtained spectrum of USP Glipizide RS.

B: GLIPIZIDE—

The retention time of the major peak in the chromatogram of the *Assay preparation* corresponds to that in the chromatogram of the *Standard preparation,* as obtained in the *Assay for glipizide.*

C: METFORMIN HYDROCHLORIDE—

The retention time of the major peak in the chromatogram of the *Assay preparation* corresponds to that in the chromatogram of the *Standard preparation,* as obtained in the *Assay for metformin hydrochloride.*

Change to read:

Dissolution ⟨711⟩**—**

•TEST 1—•(RB 1-Dec-2009)

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

Apparatus 2: 50 rpm.

Times: 45 minutes for glipizide, 30 minutes for metformin hydrochloride.

Determine the amount of glipizide ($C_{21}H_{27}N_5O_4S$) dissolved by employing the following method.

Buffer solution—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, and mix.

Mobile phase—Prepare a filtered and degassed mixture of methanol and *Buffer solution* (13 : 12). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

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

Working standard solution—Dilute the *Standard solution* with *Medium* in order to obtain a solution containing *L*/1000 mg per mL, with *L* being the glipizide tablet label claim, in mg.

Test solution—After the specified time, withdraw about 10 mL of the solution under test. Pass the solution through a 0.45-µm PVDF filter or a 1.0-µm glass fiber filter, discarding the first mL.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 220-nm detector and a 4.6-mm × 15-cm column that contains 5-µm packing L1. The flow rate is about 1.0 mL per minute. Chromatograph the *Working standard solution,* and record the peak responses as directed for *Procedure:* the relative standard deviation for replicate injections is not more than 2.0%.

Procedure—Separately inject equal volumes (about 50 µL) of the *Working standard solution* and the *Test solution* into the chromatograph, record the chromatograms running for about 8 minutes, and measure the peak response for glipizide. Calculate the amount of glipizide ($C_{21}H_{27}N_5O_4S$) dissolved by the formula:

$$\frac{r_U \times C_S \times 1000 \times 100}{r_S \times L}$$

in which r_U and r_S are the peak responses obtained from the *Test solution* and the *Working standard solution,* respectively; C_S is the concentration, in mg per mL, of glipizide in the *Working standard solution;* 1000 is the volume, in mL, of *Medium;* 100 is the conversion factor to percentage; and *L* is the tablet label claim for glipizide, in mg.

Determine the amount of metformin hydrochloride ($C_4H_{11}N_5 \cdot HCl$) dissolved by employing the following method.

Test solution—After the specified time, withdraw about 10 mL of the solution under test. Pass the solution through a 0.45-µm PVDF filter or a 1.0-µm glass fiber filter, discarding the first mL.

Procedure—Determine the amount of metformin hydrochloride dissolved by employing UV absorption at the wavelength of maximum absorbance at about 233 nm on portions of the *Test 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 metformin hydrochloride ($C_4H_{11}N_5 \cdot HCl$) dissolved by the formula:

$$\frac{A_U \times C_S \times 1000 \times 100}{A_S \times L}$$

in which A_U and A_S are the absorbances obtained from the *Test solution* and the *Working standard solution,* respectively; C_S is the concentration, in mg per mL, of the *Working standard solution;* 1000 is the volume, in mL, of *Medium;* 100 is the conversion factor to percentage; and *L* is the tablet label claim for metformin hydrochloride, in mg.

Tolerances—Not less than 80% *(Q)* of the labeled amount of $C_{21}H_{27}N_5O_4S$ is dissolved in 45 minutes. Not less than 80% *(Q)* of the labeled amount of $C_4H_{11}N_5 \cdot HCl$ is dissolved in 30 minutes.

•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 minutes for both metformin hydrochloride and glipizide.

pH 6.0 Buffer solution—Dissolve 4.3 g of octanesulfonic acid sodium salt and 6.9 g of monobasic monohydrate sodium phosphate in 1000 mL of water. Adjust with diluted sodium hydroxide to a pH of 6.00 ± 0.05.

Glipizide standard stock solution—Transfer about 25 mg of USP Glipizide RS, accurately weighed, to a 500 mL volumetric flask. Dissolve in and dilute with methanol to volume.

Working standard solution—Transfer an accurately weighed 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 per mL, where L is the tablet label claim for both metformin hydrochloride and glipizide, in mg.

Test solution—Pass a portion of the solution under test through a suitable 0.45-µm polyethersulfone filter, discarding the first few mL.

Mobile phase—Prepare a filtered and degassed mixture of methanol and *pH 6.0 Buffer solution* (1 : 1). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Chromatographic system (see Chromatography ⟨621⟩*)*—The liquid chromatograph is equipped with a 260-nm detector, a sample compartment chiller maintained at 4°, and a 4.6-mm × 25-cm column that contains packing L1. The flow rate is about 1.0 mL per minute. Chromatograph the *Working standard solution*, and record the peak responses as directed for *Procedure*: the resolution, *R,* between glipizide and metformin hydrochloride is not less than 2, and the relative standard deviation for replicate injections is not more than 2.0% for both glipizide and metformin hydrochloride.

Procedure—Separately inject equal volumes (about 20 µL) of the *Working standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the peak response for both glipizide and metformin hydrochloride. Calculate the percentage of glipizide and metformin hydrochloride dissolved by the formula:

$$\frac{r_U \times C_S \times 1000 \times 100}{r_S \times L}$$

in which r_U and r_S are the peak responses obtained for glipizide or metformin hydrochloride from the *Test solution* and the *Working standard solution,* respectively; C_S is the concentration, in mg per mL, of glipizide or metformin hydrochloride in the *Working standard solution;* 1000 is the volume, in mL, of *Medium;* 100 is the conversion factor to percentage; and L is the tablet label claim for glipizide or metformin hydrochloride, in mg.

Tolerances—Not less than 80% (Q) of the labeled amount of $C_{21}H_{27}N_5O_4S$ and of $C_4H_{11}N_5 \cdot HCl$ is dissolved in 60 minutes.● (RB 1-Dec-2009)

Uniformity of dosage units ⟨905⟩**:** meet the requirements.

Related compounds—

GLIPIZIDE—

Ammonium phosphate buffer, Solution A, Solution B, and *Chromatographic system*—Prepare as directed in the *Assay for glipizide*.

Test solution—Use the *Assay preparation,* prepared as directed in the *Assay for glipizide*.

Procedure—Inject about 50 µL of the *Test solution* into the chromatograph, record the chromatogram, and measure the peak responses. Calculate the percentage of glipizide related compound A (approximate relative retention time 0.92) and other individual impurities in the portion of Tablets taken by the formula:

$$100(1/F)(r_i / r_s)$$

in which F is the relative response factor for each impurity and is equal to 1.4 for glipizide related compound A and 1.0 for all other peaks; r_i is the peak response of each impurity; and r_s is the sum of the responses of all the peaks: not more than 2.0% of glipizide related compound A is found; not more than 0.5% of any other individual glipizide related impurity (eluting after approximately 8 minutes) is found; and not more than 1.0% total impurities, excluding glipizide related compound A, is found. [NOTE—Disregard the broad peak due to metformin that elutes before 8 minutes. Disregard any peak observed in the blank, and disregard any peak less than 0.05%.]

Chromatographic purity—

METFORMIN HYDROCHLORIDE—

Solution A, Solution B, Mobile phase, and *Chromatographic system*—Prepare as directed in the *Assay for metformin hydrochloride*.

Test solution—Use the *Assay preparation,* prepared as directed in the *Assay for metformin hydrochloride.*

Procedure—Inject about 25 µL of the *Test solution* into the chromatograph, record the chromatogram, and measure the peak responses. Calculate the percentage of each impurity in the portion of Tablets taken by the formula:

$$100(r_i / r_s)$$

in which r_i is the peak response for each impurity, and r_s is the sum of the responses of all the peaks: not more than 0.1% of any individual impurity is found; and not more than 0.5% of total impurities is found. [NOTE—Disregard any peak less than 0.05%, and disregard any peak observed in the blank.]

Assay for glipizide—

Ammonium phosphate buffer—Dissolve 2.6 g of dibasic ammonium phosphate in water, and dilute with water to 1000 mL. Adjust with ammonium hydroxide to a pH of 8.0.

Solution A—Prepare a degassed mixture of water, *Ammonium phosphate buffer,* and acetonitrile (14 : 5 : 1).

Solution B—Prepare a degassed mixture of acetonitrile, *Ammonium phosphate buffer,* and water (2 : 1 : 1).

Diluent—Use a mixture of acetonitrile and water (60 : 40).

Standard stock preparation—Transfer an accurately 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 about 20 minutes, then dilute with water to volume to obtain a solution having a known concentration of about 0.1 mg of glipizide per mL. [NOTE—The solution is stable for 2 weeks when stored at 5° protected from light.]

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

System suitability preparation—Transfer approximately 5 mg of USP Glipizide Related Compound A RS to a 500-mL volumetric flask, and fill halfway with acetonitrile. Sonicate for about 30 minutes 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 preparation* to volume.

Assay preparation—Transfer not fewer than 5 Tablets to a suitable volumetric flask, and fill halfway with *Diluent*. Sonicate for 30 minutes, and shake vigorously for another 30 minutes to dissolve. Dilute with water to volume, and mix to obtain a solution with a final glipizide concentration of about 0.0125 mg per mL. Pass a

portion of this solution through a nylon or PVDF filter having a 0.2-µm porosity, and use the filtrate. [NOTE—The solution is stable for 2 weeks when stored at 5° protected from light.]

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 223-nm detector and a 4.6-mm × 15-cm column that contains 5-µm packing L7. The flow rate is about 1.0 mL per minute. The chromatograph is programmed as follows.

Time (minutes)	*Solution A* (%)	*Solution B* (%)	Elution
0–3	100	0	isocratic
3–18	100→0	0→100	linear gradient
18–20	0	100	isocratic
20–22	0→100	100→0	linear gradient
22–30	100	0	re-equilibration

Chromatograph the *System suitability preparation* and the *Standard preparation,* and record the peak responses as directed for *Procedure*. For the *System suitability preparation,* the relative retention times are about 0.92 for glipizide related compound A and 1.0 for glipizide; the resolution, *R,* between glipizide related compound A and glipizide is greater than 1.2. For the *Standard preparation,* the relative standard deviation for replicate injections is less than 2.0%.

Procedure—Separately inject equal volumes (about 50 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the responses for the glipizide peaks. Calculate the quantity, in mg per Tablet, of glipizide ($C_{21}H_{27}N_5O_4S$) by the formula:

$$CV(r_U / r_S)/N$$

in which *C* is the concentration, in mg per mL, of USP Glipizide RS in the *Standard preparation; V* is the volume, in mL, of the *Assay preparation;* r_U and r_S are the glipizide peak responses obtained from the *Assay preparation* and the *Standard preparation,* respectively; and *N* is the number of Tablets taken to prepare the *Assay preparation.*

Assay for metformin hydrochloride—

Solution A—Prepare a 50 mM hexanesulfonic acid solution by dissolving 9.41 g of sodium 1-hexanesulfonate in 1000 mL of water, and adjusting with trifluoroacetic acid to a pH of 2.0.

Solution B—Prepare a solution of water and acetonitrile (60 : 40).

Mobile phase—Prepare a degassed mixture of water, *Solution A,* and *Solution B* (50 : 30 : 20). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Diluent pH 2.0—Prepare a mixture of water, *Solution A*, and acetonitrile (63 : 30 : 7).

Standard preparation—Dissolve an accurately weighed quantity of USP Metformin Hydrochloride RS in *Diluent pH 2.0* to obtain a solution having a known concentration of about 0.1 mg per mL.

System suitability preparation—Dissolve a suitable quantity of USP Metformin Related Compound A RS in water to obtain a solution containing about 5 µg per mL. Pipet 0.5 mL of this solution into a 50-mL volumetric flask, and dilute with the *Standard preparation* to volume.

Assay preparation—Quantitatively dilute a portion of the *Assay preparation,* obtained as directed in the *Assay for glipizide,* with *Diluent pH 2.0,* to obtain a solution having an expected concentration of about 0.1 mg of metformin hydrochloride per mL, based on the label claim.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 218-nm detector and a 4.6-mm × 15-cm column that contains 3.5-µm packing L11. The flow rate is about 1.0 mL per minute. Chromatograph the *System suitability preparation,* and record the peak responses as directed for *Procedure:* the relative retention times are about 0.26 for metformin related compound A and 1.0 for metformin; the resolution, *R,* between the two peaks is not less than 3.0; and the relative standard deviation for replicate injections, determined from the metformin peak, is less than 2.0%.

Procedure—Separately inject equal volumes (about 25 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in mg per Tablet, of metformin hydrochloride ($C_4H_{11}N_5 \cdot HCl$) by the formula:

$$CVD(r_U / r_S)/N$$

in which *C* is the concentration, in mg per mL, of USP Metformin Hydrochloride RS in the *Standard preparation; V* is the volume, in mL, of the *Assay preparation*, as prepared in the *Assay for glipizide; D* is the dilution factor of the *Assay preparation;* r_U and r_S are the peak responses obtained from the *Assay preparation* and the *Standard preparation,* respectively; and *N* is the number of Tablets used to prepare the *Assay preparation.*