Residue on ignition ⟨281⟩**:** not more than 0.1%.

Heavy metals, *Method I* ⟨231⟩**:** 0.001%.

Related compounds—

Mobile phase—Prepare a solution in water, containing 17 g of monobasic ammonium phosphate per L, adjust with phosphoric acid to a pH of 3.0, and mix.

Standard solution—Prepare a solution of USP Metformin Related Compound A RS in water having a known concentration of about 0.2 mg per mL. Transfer 1.0 mL of this solution to a 200-mL volumetric flask, dilute with *Mobile phase* to volume, and mix. [NOTE—Metformin related compound A is 1-cyanoguanidine.]

Test solution—Transfer about 500 mg of Metformin Hydrochloride, accurately weighed, to a 100-mL volumetric flask, dissolve in and dilute with *Mobile phase* to volume, and mix.

Diluted test solution—Transfer 1.0 mL of the *Test solution* to a 10-mL volumetric flask, dilute with *Mobile phase* to volume, and mix. Transfer 1.0 mL of this solution to a 100-mL volumetric flask, dilute with *Mobile phase* to volume, and mix.

Resolution solution—Prepare a solution in water containing about 0.25 mg of metformin hydrochloride and about 0.1 mg of melamine per mL. Transfer 1.0 mL of this solution to a 50-mL volumetric flask, dilute with *Mobile phase* to volume, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 218-nm detector and a 4.6-mm × 25-cm column containing packing L9. The flow rate is about 1.0 to 1.7 mL per minute. Chromatograph the *Resolution solution,* and record the peak responses as directed for *Procedure:* the resolution, *R,* between melamine and metformin is not less than 10.

Procedure—Separately inject equal volumes (about 20 µL) of the *Test solution,* the *Standard solution,* and the *Diluted test solution* into the chromatograph, record the chromatograms for not less than twice the retention time of metformin, and measure the peak areas. Calculate the percentage of metformin related compound A in the portion of Metformin Hydrochloride taken by the formula:

$$10C/W(r_U / r_S)$$

in which C is the concentration, in µg per mL, of USP Metformin Related Compound A RS in the *Standard solution; W* is the weight, in mg, of Metformin Hydrochloride taken to prepare the *Test solution;* and r_U and r_S are the metformin related compound A peak responses obtained from the *Test solution* and the *Standard solution,* respectively: not more than 0.02% of metformin related compound A is found.

Calculate the percentage of any other impurity in the portion of Metformin Hydrochloride taken by the formula:

$$0.1(r_i / r_S)$$

in which r_i is the peak response for an individual impurity obtained from the *Test solution;* and r_S is the metformin peak response obtained from the *Diluted test solution:* not more than 0.1% of any other impurity is found; and not more than 0.5% of total impurities is found.

Assay—[NOTE—To avoid overheating of the reaction medium, mix thoroughly throughout the titration, and stop the titration immediately after the endpoint has been reached.] Dissolve about 60 mg of Metformin Hydrochloride, accurately weighed, in 4 mL of anhydrous formic acid. Add 50 mL of acetic anhydride. Titrate with 0.1 N perchloric acid VS, determining the endpoint potentiometrically. Perform a blank determination, and make any necessary correction (see *Titrimetry* ⟨541⟩). Each mL of 0.1 N perchloric acid is equivalent to 8.28 mg of $C_4H_{11}N_5 \cdot HCl$.

Metformin Hydrochloride Tablets

» Metformin Hydrochloride Tablets contain not less than 95.0 percent and not more than 105.0 percent of metformin hydrochloride ($C_4H_{11}N_5 \cdot HCl$).

Packaging and storage—Preserve in tight containers. 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

Identification—

A: *Infrared Absorption* ⟨197K⟩.

Test specimen—Transfer a quantity of powdered Tablets, equivalent to about 20 mg of metformin hydrochloride, to a suitable flask, add 20 mL of dehydrated alcohol, and shake. Filter, evaporate the filtrate on a water bath to dryness, and dry the residue at 105° for 2 hours.

B: Triturate a quantity of the powdered Tablets, equivalent to about 50 mg of metformin hydrochloride, with 10 mL of water, and filter. To 5 mL of the filtrate add 1.5 mL of 5 N sodium hydroxide solution and 1 mL of a 1-naphthol solution, prepared by dissolving 1 g of 1-naphthol in a solution containing 6 g of sodium hydroxide and 16 g of anhydrous sodium carbonate in 100 mL of water. Add 0.5 mL of sodium hypochlorite TS, dropwise, and with shaking: an orange-red color is produced that darkens on standing.

C: Triturate a quantity of the powdered Tablets, equivalent to about 50 mg of metformin hydrochloride, with 10 mL of water, and filter. The filtrate meets the requirements of the tests for *Chloride* ⟨191⟩.

Dissolution ⟨711⟩**—**

TEST 1—

Medium: pH 6.8 phosphate buffer; 1000 mL.

Apparatus 1: 100 rpm.

Time: 45 minutes.

Procedure—Determine the amount of $C_4H_{11}N_5 \cdot HCl$ dissolved by employing UV absorption at the wavelength of maximum absorbance at about 233 nm on filtered portions of the solution under test, 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.*

Tolerances—Not less than 70% *(Q)* of the labeled amount of $C_4H_{11}N_5 \cdot HCl$ is dissolved in 45 minutes.

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

FOR PRODUCTS LABELED TO CONTAIN 500 MG OF METFORMIN—

Medium: pH 6.8 phosphate buffer; 1000 mL.

Apparatus 2: 50 rpm.

Time: 30 minutes.

Procedure—Proceed as directed for *Test 1.*

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

FOR PRODUCTS LABELED TO CONTAIN 850 MG OR 1000 MG OF METFORMIN—

Medium: pH 6.8 phosphate buffer; 1000 mL.

Apparatus 2: 75 rpm.

Time: 30 minutes.

Procedure—Proceed as directed for *Test 1.*

Tolerances—Not less than 75% *(Q)* of the labeled amount of $C_4H_{11}N_5 \cdot HCl$ is dissolved in 30 minutes.

TEST 3—If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 3.*

Medium: pH 6.8 phosphate buffer; 1000 mL.

Apparatus 1: 100 rpm.

Time: 60 minutes.

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

0.05 M Sodium phosphate with 1-pentanesulfonic acid solution—Dissolve 1.38 g of monobasic sodium phosphate in about 1800 mL of water. Add 3.484 g of 1-pentanesulfonic acid sodium salt, and mix. Adjust with diluted phosphoric acid to a pH of 3.00 ± 0.05. Add water to make 2000 mL, and mix.

Mobile phase—Prepare a filtered and degassed mixture of *0.05 M Sodium phosphate with 1-pentanesulfonic acid solution* and acetonitrile (19:1). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard stock solution—Transfer about 25 mg, accurately weighed, of USP Metformin Hydrochloride RS to a 100-mL volumetric flask, and add about 50 mL of *Medium*. Sonicate until dissolved, and dilute with *Medium* to volume.

Standard solution—Transfer 10.0 mL of the *Standard stock solution* to a 50-mL volumetric flask, and dilute with *Medium* to volume.

Test solution—Withdraw a portion of the solution under test, and pass through a 0.45-µm nylon filter. Dilute with *Medium,* if necessary, to obtain a concentration similar to that of the *Standard solution*.

Chromatographic system—The liquid chromatograph is equipped with a 230-nm detector and a 4.6-mm × 25-cm column that contains 5-µm packing L1. The flow rate is about 1.0 mL per minute. Chromatograph replicate injections of the *Standard solution,* and record the peak responses as directed for *Procedure:* the tailing factor is not more than 2.0; the column efficiency is not less than 1500 theoretical plates; and the relative standard deviation for replicate injections is not more than 2.0%.

Procedure—Separately inject equal volumes (about 40 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the percentage of metformin released by the formula:

$$\frac{r_U \times C_S \times 900 \times 100}{r_S \times D \times LC}$$

in which r_U and r_S are the peak responses obtained from the *Test solution* and the *Standard solution,* respectively; C_S is the concentration, in mg per mL, of metformin in the *Standard solution;* 900 is the volume, in mL, of *Medium;* 100 is the conversion factor to percentage; *D* is the dilution factor of the *Test solution;* and *LC* is the Tablet label claim, in mg.

Tolerances—Not less than 70% *(Q)* of the labeled amount of $C_4H_{11}N_5 \cdot HCl$ is dissolved in 60 minutes.

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

Related compounds—

Mobile phase, Resolution solution, and *Chromatographic system*—Proceed as directed in the test for *Related compounds* under *Metformin Hydrochloride*.

Test solution—Weigh and finely powder not fewer than 20 Tablets. Transfer a portion of the powder, equivalent to about 500 mg of metformin hydrochloride, to a 100-mL volumetric flask, dissolve in *Mobile phase,* with shaking, dilute with *Mobile phase* to volume, and mix. Filter, and use the filtrate.

Diluted test solution—Proceed as directed in the test for *Related compounds* under *Metformin Hydrochloride,* except to use the *Test solution* prepared as described herein.

Procedure—Separately inject equal volumes (about 20 µL) of the *Test solution* and the *Diluted test solution* into the chromatograph, record the chromatograms for not less than twice the retention time of metformin, and measure the peak areas.

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

$$0.1(r_i / r_S)$$

in which r_i is the peak response for each individual impurity obtained from the *Test solution;* and r_S is the metformin peak response obtained from the *Diluted test solution:* not more than 0.1% of any impurity is found; and not more than 0.6% of total impurities is found.

Assay—

Standard preparation—Prepare a solution of USP Metformin Hydrochloride RS in water having a known concentration of about 10 µg per mL.

Assay preparation—Weigh and finely powder not fewer than 20 Tablets. Transfer an accurately weighed portion of the powder, equivalent to about 100 mg of metformin hydrochloride, to a 100-mL volumetric flask. Add 70 mL of water, shake by mechanical means for 15 minutes, dilute with water to volume, and filter, discarding the first 20 mL of the filtrate. Dilute 10.0 mL of the filtrate with water to 100.0 mL, and dilute 10.0 mL of the resulting solution with water to 100.0 mL.

Procedure—Concomitantly determine the absorbances of the *Standard preparation* and the *Assay preparation,* in 1-cm cells, at the wavelength of maximum absorbance at about 232 nm, with a suitable spectrophotometer, using water as a blank. Calculate the quantity, in mg, of metformin hydrochloride ($C_4H_{11}N_5 \cdot HCl$) in the portion of Tablets taken by the formula:

$$10C(A_U / A_S)$$

in which *C* is the concentration, in µg per mL, of USP Metformin Hydrochloride RS in the *Standard preparation;* and A_U and A_S are the absorbances obtained from the *Assay preparation* and the *Standard preparation,* respectively.

Metformin Hydrochloride Extended-Release Tablets

DEFINITION

Metformin Hydrochloride Extended-Release Tablets contain NLT 90.0% and NMT 110.0% of the labeled amount of metformin hydrochloride ($C_4H_{11}N_5 \cdot HCl$).

IDENTIFICATION

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

ASSAY

- **PROCEDURE**

Buffer solution: 0.5 g/L of sodium heptanesulfonate and 0.5 g/L of sodium chloride in water. Before final dilution, adjust with 0.06 M phosphoric acid to a pH of 3.85.

Mobile phase: Acetonitrile and *Buffer solution* (1:9). [NOTE—To improve the separation, the composition of acetonitrile and *Buffer solution* may be changed to 1:19, if necessary.]

Diluent: 1.25% solution of acetonitrile in water

Standard solution: (L/4000) mg/mL of USP Metformin Hydrochloride RS in *Diluent*, where L is the labeled quantity, in mg, of metformin hydrochloride in each Tablet

System suitability stock solution: 12.5 µg/mL of each of USP Metformin Related Compound B RS and USP Metformin Related Compound C RS in *Diluent*

System suitability solution: Dilute 0.5 mL of the *System suitability stock solution* with the *Standard solution* to 50 mL.

Sample stock solution: Finely powder NLT 10 Tablets. Transfer powder, equivalent to the average Tablet weight, to a homogenization vessel, and add 500 mL of 10% acetonitrile solution. Alternately, homogenize and allow to soak un-