

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.

• USP REFERENCE STANDARDS <11>

USP Glyburide RS

USP Glyburide Related Compound A RS

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

$C_{16}H_{17}ClN_2O_4S$ 368.84

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

• A. INFRARED ABSORPTION <197F>

• B. LIMIT OF DIETHYLENE GLYCOL AND ETHYLENE GLYCOL

Standard solution: 2.0 mg/mL of USP Glycerin RS, 0.050 mg/mL of USP Ethylene Glycol RS, 0.050 mg/mL of USP Diethylene Glycol RS, and 0.10 mg/mL of 2,2,2-trichloroethanol (internal standard) in methanol

Sample solution: 50 mg/mL of Glycerin and 0.10 mg/mL of 2,2,2-trichloroethanol (internal standard) in methanol

Chromatographic system

(See *Chromatography* <621>, *System Suitability*.)

Mode: GC

Detector: Flame ionization

Column: 0.53-mm $\times$ 30-m fused-silica analytical column coated with 3.0- μ m G43 stationary phase, and a deactivated split liner with glass wool

Temperature

Injector: 220°

Detector: 250°

Column: See the temperature program table.

Initial Temperature (°)	Temperature Ramp (°/min)	Final Temperature (°)	Hold Time at Final Temperature (min)
100	—	100	4
100	50	120	10
120	50	220	6

Carrier gas: Helium

Injection size: 1.0 μ L

Flow rate: 4.5 mL/min

Injection type: Split ratio, about 10:1

System suitability

Sample: *Standard solution*

[NOTE—The relative retention times for ethylene glycol, 2,2,2-trichloroethanol, diethylene glycol, and glycerin are about 0.3, 0.6, 0.8 and 1.0, respectively.]

Suitability requirements

Resolution: NLT 1.5 between diethylene glycol and glycerin

Analysis

Sample: *Sample solution*

Acceptance criteria: If a peak at the retention times for the diethylene glycol or ethylene glycol is present in the *Sample solution*, the peak response ratio relative to 2,2,2-trichloroethanol is NMT the peak response ratio for diethylene glycol or ethylene glycol relative to 2,2,2-trichloroethanol in the *Standard solution*; NMT 0.10% each for diethylene glycol and ethylene glycol is found.

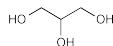
• **C.** Examine the chromatograms obtained in *Identification test B*. The retention time of the glycerin peak of the *Sample solution* corresponds to that obtained in the *Standard solution*.

ASSAY

• PROCEDURE

Sodium periodate solution: Dissolve 60 g of sodium metaperiodate in sufficient water containing 120 mL of 0.1 N sulfuric acid to make 1000 mL. Do not heat to dissolve the periodate. If the solution is not clear, pass through a sintered-glass filter. Store the solution in a glass-stoppered, light-resistant container. Test the suitability of this solution as follows. Pipet 10 mL into a 250-mL volumetric flask, and dilute with water to volume. To 550 mg of Glycerin dissolved in 50 mL of water, add 50 mL of the diluted periodate solution with a pipet. For a blank, pipet 50 mL of the solution into a flask containing 50 mL of water. Allow the solutions to stand for 30 min, then to each add 5 mL of hydrochloric acid and 10 mL of potassium iodide TS, and rotate to mix. Allow to stand for 5 min, add 100 mL of water, and titrate with 0.1 N sodium thiosulfate, shaking continuously and adding 3 mL of starch TS as the endpoint

Glycerin



$C_3H_8O_3$

1,2,3-Propanetriol;
Glycerol [56-81-5].

92.09

DEFINITION

Glycerin contains NLT 99.0% and NMT 101.0% of $C_3H_8O_3$, calculated on the anhydrous basis.

IDENTIFICATION

[NOTE—Compliance is determined by meeting the requirements for *Identification tests A, B, and C*.]

is approached. The ratio of the volume of 0.1 N sodium thiosulfate required for the glycerin–periodate mixture to that required for the blank should be between 0.750 and 0.765.

Analysis: Transfer 400 mg of Glycerin to a 600-mL beaker, dilute with 50 mL of water, add bromothymol blue TS, and acidify with 0.2 N sulfuric acid to a definite green or greenish yellow color. Neutralize with 0.05 N sodium hydroxide to a definite blue endpoint, free from green color. Prepare a blank containing 50 mL of water, and neutralize in the same manner. Pipet 50 mL of the *Sodium periodate solution* into each beaker, mix by swirling gently, cover with a watch glass, and allow to stand for 30 min at room temperature (not exceeding 35°) in the dark or in subdued light. Add 10 mL of a mixture of equal volumes of ethylene glycol and water, and allow to stand for 20 min. Dilute each solution with water to 300 mL, and titrate with 0.1 N sodium hydroxide VS to a pH of 8.1 ± 0.1 for the specimen under assay and 6.5 ± 0.1 for the blank, using a pH meter. Each mL of 0.1 N sodium hydroxide, after correction for the blank, is equivalent to 9.210 mg of $C_3H_8O_3$.

Acceptance criteria: 99.0%–101.0% on the anhydrous basis

IMPURITIES

Inorganic Impurities

- **CHLORIDE AND SULFATE**, *Chloride* <221>: A 7.0-g portion shows no more chloride than corresponds to 0.10 mL of 0.020 N hydrochloric acid (NMT 10 ppm).
- **CHLORIDE AND SULFATE**, *Sulfate* <221>: A 10-g portion shows no more sulfate than corresponds to 0.20 mL of 0.020 N sulfuric acid (NMT 20 ppm).

Delete the following:

- **HEAVY METALS** <231>
Analysis: Mix 4.0 g with 2 mL of 0.1 N hydrochloric acid, and dilute with water to 25 mL.
Acceptance criteria: NMT 5 ppm (Official 1-Jan-2018)
- **RESIDUE ON IGNITION** <281>: Heat 50 g in an open, shallow 100-mL porcelain dish until it ignites, and allow it to burn without further application of heat in a place free from drafts. Cool, moisten the residue with 0.5 mL of sulfuric acid, and ignite to constant weight: the weight of the residue does not exceed 5 mg (0.01%).

Organic Impurities

• PROCEDURE 1: RELATED COMPOUNDS

System suitability solution: 0.5 mg/mL each of USP Diethylene Glycol RS and USP Glycerin RS

Sample solution: 50 mg/mL of Glycerin

Chromatographic system

(See *Chromatography* <621>, *System Suitability*.)

Mode: GC

Detector: Flame ionization

Column: 0.53-mm $\times$ 30-m fused-silica analytical column coated with 3.0- μ m G43 stationary phase, and an inlet liner having an inverted cup or spiral structure

Temperature

Injector: 220°

Detector: 250°

Column: See the temperature program table below.

Initial Temperature (°)	Temperature Ramp (°/min)	Final Temperature (°)	Hold Time at Final Temperature (min)
100	—	100	—
100	7.5	220	4

Carrier gas: Helium

Injection size: 0.5 μ L

Linear velocity: 38 cm/s

Injection type: Split ratio, about 10:1

System suitability

Sample: *System suitability solution*

Suitability requirements

Resolution: NLT 7.0 between diethylene glycol and glycerin

Analysis

Sample: *Sample solution*

Calculate the percentage of each impurity, excluding any solvent peaks and diethylene glycol, in the portion of Glycerin taken:

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

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

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

Acceptance criteria

Individual impurities: NMT 0.1%

Total impurities: NMT 1.0%

• PROCEDURE 2: LIMIT OF CHLORINATED COMPOUNDS

Sample: 5 g of Glycerin

Analysis: Transfer the *Sample* into a dry, round-bottom, 100-mL flask. Add 15 mL of morpholine, and connect the flask by a ground joint to a reflux condenser. Reflux gently for 3 h. Rinse the condenser with 10 mL of water, receiving the washings in the flask, and cautiously acidify with nitric acid. Transfer the solution to a suitable comparison tube, add 0.50 mL of silver nitrate TS, and dilute with water to 50.0 mL.

Acceptance criteria: The turbidity is not greater than that of a blank to which 0.20 mL of 0.020 N hydrochloric acid has been added, the refluxing being omitted (NMT 30 ppm of Cl).

• PROCEDURE 3: FATTY ACIDS AND ESTERS

Sample solution: Mix 50 g of Glycerin with 50 mL of freshly boiled water and 5 mL of 0.5 N sodium hydroxide VS. Boil the mixture for 5 min, cool, and add phenolphthalein TS.

Analysis: Titrate the excess alkali with 0.5 N hydrochloric acid VS. Perform a blank determination (see *Titrimetry* <541>, *Residual Titrations*).

Acceptance criteria: NMT 1 mL of 0.5 N sodium hydroxide is consumed.

SPECIFIC TESTS

- **COLOR:** When viewed downward against a white surface in a 50-mL color-comparison tube, the color is not darker than the color of a standard made by diluting 0.40 mL of ferric chloride CS with water to 50 mL and similarly viewed in a color-comparison tube of approximately the same diameter and color as that containing the Glycerin.
- **SPECIFIC GRAVITY** <841>: NLT 1.249
- **WATER DETERMINATION**, *Method I* <921>: NMT 5.0%

ADDITIONAL REQUIREMENTS

- **PACKAGING AND STORAGE:** Preserve in tight containers.

• USP REFERENCE STANDARDS <11>

USP Diethylene Glycol RS

USP Ethylene Glycol RS

USP Glycerin RS

1,2,3-Propanetriol.

$C_3H_8O_3$ 92.10

Glycerin Ophthalmic Solution

» Glycerin Ophthalmic Solution is a sterile, anhydrous solution of Glycerin, containing not less than 98.5 percent of glycerin ($C_3H_8O_3$). It may contain one or more suitable antimicrobial preservatives. [NOTE—In the preparation of this Ophthalmic Solution, use Glycerin that has a low water content, in order that the Ophthalmic Solution may comply with the *Water* limit. This may be ensured by using Glycerin having a specific gravity of not less than 1.2607, corresponding to a concentration of 99.5 percent.]

NOTE—Do not use the Ophthalmic Solution if it contains crystals, or is cloudy or discolored, or contains a precipitate.

Packaging and storage—Preserve in tight containers of glass or plastic, containing not more than 15 mL, protected from light. The container or individual carton is sealed and tamper-proof so that sterility is ensured at time of first use.

USP Reference standards <11>—

USP Glycerin RS

Identification—It responds to the *Identification* test under *Glycerin*.

Sterility Tests <71>: meets the requirements.

pH <791>: between 4.5 and 7.5, determined potentiometrically in a solution prepared by the addition of 5 mL of Sodium Chloride Injection to 5 mL of Ophthalmic Solution.

Water Determination, Method I <921>: not more than 1.0%.

Assay—Transfer an accurately measured volume of Ophthalmic Solution, equivalent to about 3 g of glycerin, to a 500-mL volumetric flask, dilute with water to volume, and mix. Transfer a 3-mL portion to a conical flask, add 100.0 mL of a solution of potassium periodate (prepared by dissolving 3 g of potassium periodate in about 500 mL of warm water, cooling to room temperature, and then diluting with water to 1000 mL), swirl, and allow to stand at room temperature for 10 minutes. Add 4 g of sodium bicarbonate and 2 g of potassium iodide, and titrate immediately with 0.1 N potassium arsenite VS, adding 3 mL of starch TS as the endpoint is approached. Perform a blank determination, using water in place of the Ophthalmic Solution, and note the difference in volumes required. Each mL of 0.1 N potassium arsenite is equivalent to 2.303 mg of glycerin ($C_3H_8O_3$).

Glycerin Oral Solution

» Glycerin Oral Solution contains not less than 95.0 percent and not more than 105.0 percent of the labeled amount of glycerin ($C_3H_8O_3$).

Packaging and storage—Preserve in tight containers.

Identification—Heat a few drops with about 500 mg of potassium bisulfate in a test tube: pungent vapors of acrolein are evolved.

pH <791>: between 5.5 and 7.5.

Assay—Transfer an accurately measured volume of Oral Solution, equivalent to about 3 g of glycerin, to a 500-mL volumetric flask, dilute with water to volume, and mix. Transfer

a 3-mL portion to a conical flask, add 100.0 mL of a solution of potassium periodate (prepared by dissolving 3 g of potassium periodate in about 500 mL of warm water, cooling to room temperature, and then diluting with water to 1000 mL), swirl, and allow to stand at room temperature for 10 minutes. Add 4 g of sodium bicarbonate and 2 g of potassium iodide, and titrate immediately with 0.1 N potassium arsenite VS, adding 3 mL of starch TS as the endpoint is approached. Perform a blank determination, using water in place of the Oral Solution, and note the difference in volumes required. Each mL of 0.1 N potassium arsenite is equivalent to 2.303 mg of glycerin ($C_3H_8O_3$).

Glycerin Suppositories

» Glycerin Suppositories contain Glycerin solidified with Sodium Stearate. [NOTE—If preferred, the Sodium Stearate for Glycerin Suppositories may be prepared during the making of the Suppositories by the direct reaction between Stearic Acid and Sodium Bicarbonate, Sodium Carbonate, or Sodium Hydroxide, these being taken in the correct proportion.] Glycerin Suppositories contain not less than 75.0 percent and not more than 90.0 percent, by weight, of glycerin ($C_3H_8O_3$).

Packaging and storage—Preserve in well-closed containers.

USP Reference standards <11>—

USP Stearic Acid RS

Identification—

A: Dissolve 1 g of sodium borate in 100 mL of water, add 25 drops of phenolphthalein TS, and mix. To a test tube containing 0.5 mL of this solution add 2 drops of 1 Suppository that has been melted: the pink solution becomes colorless, and when it is heated the pink color reappears.

B: Disperse 12 Suppositories in about 125 mL of water in a 250-mL beaker on a hot plate. Cool, add 1.5 mL of hydrochloric acid, and pour the mixture into a 250-mL separator. Extract with 75 mL of hexanes, discarding the lower aqueous layer and collecting the organic layer in a beaker. Evaporate with the aid of a steam bath to near dryness: the IR absorption spectrum of a mineral oil dispersion of the residue so obtained exhibits maxima only at the same wavelengths as those of a mineral oil dispersion of USP Stearic Acid RS.

Water Determination, Method I <921>: not more than 15.0%.

Assay—Transfer an accurately weighed quantity of Suppositories, equivalent to about 250 mg of glycerin, to a 250-mL volumetric flask. Dissolve in water, dilute with water to volume, and mix. Pipet 5 mL of this solution into a 250-mL conical flask, and add 50.0 mL of a reagent prepared by mixing 40 mL of dilute sulfuric acid (1 in 20) with 60 mL of potassium periodate solution (1 in 1000) acidified with 3 to 5 drops of sulfuric acid. Heat the solution on a steam bath for 15 minutes, cool to room temperature, and add 1 g of potassium iodide. Allow the flask to stand for 5 minutes, and titrate with 0.02 N sodium thiosulfate VS, adding 3 mL of starch TS as the endpoint is approached. Perform a blank determination, using water in place of Suppositories, and note the difference in volumes required. Each mL of the difference in volume of 0.02 N sodium thiosulfate consumed is equivalent to 0.4604 mg of glycerin ($C_3H_8O_3$).