**Mobile phase**—Prepare a filtered mixture of water, acetonitrile, phosphoric acid, and triethylamine (1480: 280:15:3). Make adjustments if necessary (see System Suitability under Chromatography (621)).

Lisinopril standard preparation—Dissolve an accurately weighed quantity of USP Lisinopril RS in Buffer solution to obtain a solution having a known concentration of about 0.5 mg per mL.

Hydrochlorothiazide standard preparation—Dissolve an accurately weighed quantity of USP Hydrochlorothiazide RS in methanol to obtain a solution having a known concentration of about 3.12 mg per mL.

Lisinopril related compound A standard preparation—Dissolve an accurately weighed quantity of USP Lisinopril Related Compound A RS in methanol to obtain a solution having a known concentration of about 0.05 mg per mL.

Benzothiadiazine related compound A standard preparation—Dissolve an accurately weighed quantity of USP Benzothiadiazine Related Compound A RS in methanol to obtain a solution having a known concentration of about 0.016 mg per mL.

Combined standard preparation—Dilute appropriate amounts of each of the above mentioned standard preparations quantitatively, and stepwise if necessary, with Buffer solution to obtain a Combined standard solution having a known concentration of about 0.1 mg per mL of USP Lisinopril RS; 0.125 mg per mL of USP Hydrochlorothiazide RS; 0.002 mg per mL of USP Lisinopril Related Compound A RS; and 0.0013 mg per mL of USP Benzothiadiazine Related Compound A RS. [NOTE—In the case of Tablet strengths 20/12.5 of lisinopril and hydrochlorothiazide, the concentration of lisinopril and lisinopril related compound A in the Combined standard solution is 0.2 and 0.004 mg per mL, respectively.]

Assay stock preparation—Transfer 10 tablets to a suitable volumetric flask, add Buffer solution (0.25 mL per mg of total lisinopril), sonicate for 5 minutes, and then add methanol (0.5 mL per mg of total lisinopril). Sonicate for an additional 10 minutes. Add more Buffer solution (0.75 mL per mg of total lisinopril), and mix using a mechanical shaker for 20 minutes. Dilute with water to volume to obtain a solution having a known concentration of 0.4 mg per mL of lisinopril and 0.05 mg per mL of hydrochlorothiazide for Tablet strengths of 10/12.5 and 20/25 of lisinopril and hydrochlorothiazide. In the case of Tablet strengths 20/12.5 of lisinopril and hydrochlorothiazide, dilute with water to obtain a concentration of lisinopril and hydrochlorothiazide of 0.4/0.25 mg per mL.

Assay preparation—Dilute the Assay stock preparation quantitatively with Buffer solution to obtain a solution having a final concentration of about 0.1 mg per mL of lisinopril and 0.12 mg per mL of hydrochlorothiazide for Tablet strengths of 10/12.5 and 20/25 of lisinopril and hydrochlorothiazide. In the case of Tablet strengths 20/12.5 of lisinopril and hydrochlorothiazide, the concentration of lisinopril and hydrochlorothiazide is 0.2/0.125 mg per mL. Pass a portion of this solution through a filter having a 0.45-µm or finer porosity, and use the filtrate.

Chromatographic system (see Chromatography (621))—The liquid chromatograph is equipped with a 215-nm detector and a 4.6-mm x 15-cm column that contains S-5 µm packing L7. The flow rate is about 1.5 mL per minute, and the run time is about 10 minutes. Use the Combined standard preparation, and record the peak responses as directed for Procedure: the resolution, R, between lisinopril and benzothiadiazine related compound A is greater than 3.0 and between hydrochlorothiazide and benzothiadiazine related compound A is greater than 4.0; the tailing factor for lisinopril and hydrochlorothiazide peaks is less than 2; and the relative standard deviation for replicate injections is not more than 2.0% for lisinopril and hydrochlorothiazide peaks.

Procedure—Separately inject equal volumes (about 10 µL) of the Combined standard preparation and the Assay preparation into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the percentage of lisinopril (C_{20}H_{23}N_{1}O_{5}S) and hydrochlorothiazide (C_{15}H_{17}ClN_{2}O_{5}S) based on the label claim, in the portion of Tablets taken by the formula:

\[
100(C_t / C_0)(r_t / r_i)
\]

in which C_t is the concentration, in mg per mL, of USP Lisinopril RS or USP Hydrochlorothiazide RS in the Combined standard preparation; C_0 is the concentration, in mg per mL, of lisinopril or hydrochlorothiazide in the Assay preparation based on the label claim; and r_t and r_i are the peak responses obtained from the Assay preparation and the Standard preparation, respectively.

**Lithium Carbonate**

Li$_2$CO$_3$: 73.89

Carbonic acid, dilithium salt.

Dilithium carbonate [554-13-2].

Li$_2$CO$_3$: 73.89

Carbonic acid, dilithium salt.

Dilithium carbonate [554-13-2].

» Lithium Carbonate contains not less than 99.0 percent of Li$_2$CO$_3$, calculated on the dried basis.

**Packaging and storage**—Preserve in well-closed containers.

**Identification**—

A: It effervescences upon the addition of an acid, yielding a colorless gas which, when passed into calcium hydroxide TS, immediately causes a white precipitate to form.

B: When moistened with hydrochloric acid, it imparts an intense crimson color to a nonluminous flame.

**Reaction**—A saturated solution is alkaline to litmus.

**Loss on drying** (731)—Dry it at 200° for 4 hours: it loses not more than 1.0% of its weight.

**Insoluble substances**—Transfer 10 g to a 250-mL beaker, add 50 mL of water, then add slowly 50 mL of 6 N hydrochloric acid. Cover with a watch glass, and boil the solution for 1 hour. Filter the solution through a dried, tared filtering crucible fitted with a glass-fiber filter disk, using suction. Wash the filter with hot water until the last washing is free from chloride when tested with silver nitrate TS. Dry the crucible in an oven at 110° for 1 hour: the weight of the residue is not more than 0.02% of the weight of Lithium Carbonate taken.

**Chloride** (221)—To 500 mg of it add 1.2 mL of nitric acid, dilute with water to 50 mL, and add 1 mL of silver nitrate TS; any turbidity formed is not greater than that produced in a similarly treated control solution containing 0.50 mL of 0.020 N hydrochloric acid (0.07%).

**Sulfate** (221)—Dissolve 1.0 g in 10 mL of 3 N hydrochloric acid, dilute with water to 40 mL, and add 1 mL of barium chloride TS. Prepare a standard solution of equal volume containing 1.0 mL of 0.020 N sulfuric acid, 1 mL of 3 N hydrochloric acid, and 1 mL of barium chloride TS. The turbidity produced in the test solution, after 3 minutes, is not greater than that produced in the standard solution (0.1%).

**Aluminum and iron**—Dissolve 500 mg in 10 mL of water by the dropwise addition, with agitation, of hydrochloric acid. Boil the solution, then cool it, and to 5 mL of the solution add 6 N ammonium hydroxide until the reaction is alkaline: no turbidity or precipitate is observed.

**Calcium**—Suspend 5.0 g in 50 mL of water, and add a slight excess of 3 N hydrochloric acid. Boil the clear solution to expel carbon dioxide, add 5 mL of ammonium oxalate TS, render alkaline with 6 N ammonium hydroxide, and allow to stand for 4 hours. Filter through a filtering crucible, and wash with warm water until the last washing yields no turbidity with calcium chloride TS. Place the crucible in a beaker, cover it with water, add 3 mL of sulfuric acid, heat to 70°, and titrate with 0.10 N potassium permanganate to a pale pink color that persists for 30 seconds. Not more than 3.76 mL of 0.10 N potassium permanganate is consumed (0.15%).

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Sodium—

Standard preparation—Dissolve 1.271 g of sodium chloride, previously dried at 130° to constant weight, in water in a 1000-mL volumetric flask, dilute with water to volume, and mix. Each mL contains 500 µg of Na.

Stock solution—Suspending 20.0 g of Lithium Carbonate in 100 mL of water, cautiously add 50.0 mL of hydrochloric acid, transfer to a 200-mL volumetric flask, dilute with water to volume, and mix.

Test preparation—Pipet 5 mL of Stock solution into a 100-mL volumetric flask, add water to volume, and mix.

Control solution—Pipet 5 mL of Stock solution and 1 mL of Standard preparation into a 100-mL volumetric flask, add water to volume, and mix.

Procedure—Set a suitable flame photometer for maximum emission at about 589 nm, using the Control solution. Measure the emission intensities of the Test preparation at 580 nm and 589 nm. The difference between the intensities observed at 580 nm and 589 nm for the Test preparation does not exceed the difference between the intensities observed at 589 nm for the Test preparation and the Control solution, respectively. The sodium limit is 0.1%.

Heavy metals (231)—Dissolve 1g in 10 mL of 3 N hydrochloric acid, and dilute with water to 25 mL: the limit is 0.002%.

Assay—Dissolve about 1g of Lithium Carbonate, accurately weighed, in 50.0 mL of 1 N sulfuric acid VS, add methyl orange TS, and titrate the excess acid with 1 N sodium hydroxide VS. Perform a blank determination (see Residual Titrations under Titrimetry (541)). Each mL of 1 N sulfuric acid is equivalent to 36.95 mg of Li₂CO₃.

Lithium Carbonate Capsules

Lithium Carbonate Capsules contain not less than 98.0%, and not more than 102.0% of the labeled amount of Li₂CO₃.

Packaging and storage—Preserve in well-closed containers.

USP Reference standards (11)—USP Lithium Carbonate RS

Identification—A portion of the Capsule contents responds to the Identification tests under Lithium Carbonate.

Dissolution (711)—

Medium: water; 900 mL.

Apparatus 1: 100 rpm.

Time: 30 minutes.

Procedure—Determine the amount of Li₂CO₃ dissolved in filtered portions of the solution under test with a suitable flame photometer, as directed in the Assay.

Tolerances—Not less than 80% (Q) of the labeled amount of Li₂CO₃ is dissolved in 30 minutes.

Uniformity of dosage units (905): meet the requirements.

Assay—

Standard preparation—Transfer to a 100-mL volumetric flask about 30 mg of USP Lithium Carbonate RS, accurately weighed. Add about 20 mL of water and 0.5 mL of hydrochloric acid, shake until dissolved, dilute with water to volume, and mix.

Pipet 20 mL of the resulting solution into a 1000-mL volumetric flask, add about 800 mL of water and 20 mL of a suitable surfactant solution, appropriately diluted, dilute with water to volume, and mix.

Assay preparation—Empty as completely as possible the contents of not less than 20 Capsules. Weigh accurately a portion of the powder, equivalent to about 600 mg of lithium carbonate, and transfer to a 1000-mL volumetric flask. Add 40 mL of water and 5 mL of hydrochloric acid, shake until the sample is well disintegrated, dilute with water to volume, and mix. Pipet 10 mL of the resulting solution into a 1000-mL volumetric flask, add about 800 mL of water and 20 mL of the surfactant solution, dilute with water to volume, and mix.

Procedure—Employ a suitable flame photometer, and adjust the instrument with the surfactant solution. Aspirate into the photometer the Standard preparation and the Assay preparation, and measure the emission at about 671 nm. Calculate the quantity, in mg, of Li₂CO₃ in the portion of Capsules taken by the formula:

\[
100C(A / S) \
\]

in which C is the concentration, in µg per mL, of USP Lithium Carbonate RS in the Standard preparation; and A and S are the photometer readings of the Assay preparation and the Standard preparation, respectively.

Lithium Carbonate Tablets

Definition

Lithium Carbonate Tablets contain NLT 95.0% and NMT 105.0% of the labeled amount of Li₂CO₃.

Identification

A portion of the powdered Tablets meets the requirements of the following tests.

A. It effervesces upon the addition of an acid, yielding a colorless gas that, when passed into calcium hydroxide TS, immediately causes a white precipitate to form.

B. When moistened with hydrochloric acid, it imparts an intense crimson color to a nonluminous flame.

Assay

Procedure

Standard solution: Transfer 30 mg of USP Lithium Carbonate RS to a 100-mL volumetric flask, and add 20 mL of water and 0.5 mL of hydrochloric acid. Shake until dissolved, and dilute with water to volume. Pipet 20 mL of the resulting solution into a 1000-mL volumetric flask, add 800 mL of water and 20 mL of a suitable surfactant solution, and dilute with water to volume.

Sample solution: Powder NLT 20 Tablets. Transfer a portion of powder, nominally equivalent to 600 mg of lithium carbonate, into a 1000-mL volumetric flask, add 40 mL of water and 5 mL of hydrochloric acid, shake until the solid is well disintegrated, and dilute with water to volume. Pipet 10 mL of the resulting solution into a 1000-mL volumetric flask, add 800 mL of water and 20 mL of the surfactant solution, and dilute with water to volume.

Spectrophotometric conditions

Mode: Flame photometer

Analytical wavelength: About 671 nm

[Note—Adjust the instrument with the surfactant solution.]

Analysis

Samples: Standard solution and Sample solution

Calculate the percentage of Li₂CO₃ in the portion of Tablets taken:

\[
\text{Result} = \left( \frac{r_1}{r_2} \right) \times (C_i / C_0) \times 100 \\
\]

\[
r_1 \quad = \text{peak response from the Sample solution} \\
r_2 \quad = \text{peak response from the Standard solution} \\
C_i \quad = \text{concentration of the Standard solution (mg/mL)} \\
C_0 \quad = \text{nominal concentration of lithium carbonate in the Sample solution (mg/mL)} 
\]