⟨251⟩ LEAD

The imposition of stringent limits on the amounts of lead that may be present in pharmaceutical products has resulted in the use of two methods, of which the one set forth in this chapter depends upon extraction of lead by solutions of dithizone.

Select all reagents for this test to have as low a content of lead as practicable, and store all reagent solutions in containers of borosilicate glass. Thoroughly rinse all glassware with warm dilute nitric acid (1 in 2), followed by water.

SPECIAL REAGENTS

Ammonia-cyanide solution: Dissolve 2 g of potassium cyanide in 15 mL of ammonium hydroxide, and dilute with water to 100 mL.

Ammonium citrate solution: Dissolve 40 g of citric acid in 90 mL of water. Add 2 or 3 drops of phenol red TS, then cautiously add ammonium hydroxide until the solution acquires a reddish color. Remove any lead that may be present by extracting the solution with 20-mL portions of *Dithizone extraction solution* (see below), until the dithizone solution retains its orange-green color.

Diluted standard lead solution: Dilute an accurately measured volume of standard lead solution TS (containing 10 µg of lead per mL), with 9 volumes of dilute nitric acid (1 in 100) to obtain a solution that contains 1 µg of lead per mL.

Dithizone extraction solution: Dissolve 30 mg of dithizone in 1000 mL of chloroform, and add 5 mL of alcohol. Store the solution in a refrigerator.

Before use, shake a suitable volume of the dithizone extraction solution with about half its volume of dilute nitric acid (1 in 100), discarding the nitric acid.

Hydroxylamine hydrochloride solution: Dissolve 20 g of hydroxylamine hydrochloride in sufficient water to make approximately 65 mL. Transfer to a separator, add 5 drops of thymol blue TS, then add ammonium hydroxide until the solution assumes a yellow color. Add 10 mL of sodium diethyldithiocarbamate solution (1 in 25), mix, and allow to stand for 5 min. Extract this solution with successive 10- to 15-mL portions of chloroform until a 5-mL portion of the chloroform extract does not assume a yellow color when shaken with cupric sulfate TS. Add 3 N hydrochloric acid until the solution is pink (if necessary, add 1 or 2 drops more of thymol blue TS), then dilute with water to 100 mL.

Potassium cyanide solution: Dissolve 50 g of potassium cyanide in sufficient water to make 100 mL. Remove the lead from this solution by extraction with successive portions of *Dithizone extraction solution*, as described in *Ammonium citrate solution*, then extract any dithizone remaining in the cyanide solution by shaking with chloroform. Finally, dilute the cyanide solution with sufficient water so that each 100 mL contains 10 g of potassium cyanide.

Standard dithizone solution: Dissolve 10 mg of dithizone in 1000 mL of chloroform. Keep the solution in a glass-stoppered, lead-free bottle, suitably wrapped to protect it from light, and store in a refrigerator.

PROCEDURE

Test preparation or Sample solution

[NOTE—If, in the following preparation, the substance under test reacts too rapidly and begins charring with 5 mL of sulfuric acid before heating, instead use 10 mL of cooled dilute sulfuric acid (1 in 2), and add a few drops of hydrogen peroxide before heating.]

Where the monograph does not specify preparation of a solution, prepare a *Test preparation* or *Sample solution* as follows. [**CAUTION**—*Exercise safety precautions in this procedure, because some substances may react with explosive violence when digested with hydrogen peroxide.*]

Transfer 1.0 g of the substance under test to a suitable flask, add 5 mL of sulfuric acid and a few glass beads, and digest on a hot plate in a hood until charring begins. Other suitable means of heating may be substituted. (Add additional sulfuric acid, if necessary, to wet the substance completely, but do not add more than a total of 10 mL.) Add, dropwise and with caution, 30% hydrogen peroxide, allowing the reaction to subside and heat between drops. Add the first few drops very slowly, mix carefully to prevent a rapid reaction, and discontinue heating if foaming becomes excessive. Swirl the solution in the flask to prevent unreacted substance from caking on the walls of the flask.

[NOTE—Add peroxide whenever the mixture turns brown or darkens.]

Continue the digestion until the substance is completely destroyed, copious fumes of sulfur trioxide are evolved, and the solution is colorless. Cool, and cautiously add 10 mL of water. Evaporate until sulfur trioxide again is evolved, and cool. Repeat this procedure with another 10 mL of water to remove any traces of hydrogen peroxide. Cautiously dilute with 10 mL of water, and cool.

Analysis: Transfer the *Test preparation* or *Sample solution*, rinsing with 10 mL of water, or the volume of the prepared sample specified in the monograph to a separator, and, unless otherwise directed in the monograph, add 6 mL of *Ammonium citrate solution* and 2 mL of *Hydroxylamine hydrochloride solution*. (For the determination of lead in iron salts, use 10 mL of *Ammonium citrate solution*.) Add 2 drops of phenol red TS, and make the solution just alkaline (red in color) by the addition of ammonium hydroxide. Cool the solution if necessary, and add 2 mL of *Potassium cyanide solution*. Immediately extract the solution with 5-mL portions of *Dithizone extraction solution*, draining off each extract into another separator, until the dithizone solution retains its green color. Shake the combined dithizone solutions for 30 s with 20 mL of dilute nitric acid (1 in 100), and discard the chloroform layer. Add to the acid solution 5.0 mL of *Standard dithizone solution* and 4 mL of *Ammonia-cyanide solution*, and shake for 30 s.

Acceptance criteria: The color of the chloroform layer is of no deeper shade of violet than that of a control made with a volume of *Diluted standard lead solution* equivalent to the amount of lead permitted in the sample under examination and made with the same quantities of the same reagents and in the same manner as in the test with the sample.