The United States Pharmacopeia

TWENTY-FIRST REVISION

Official from January 1, 1985

The National Formulary

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United States Pharmacopeial Convention, Inc.
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container, observing precautions against contact with water or moist atmosphere. Adjust the concentration of the reagent so that the titration volume approaches but does not exceed the capacity of the container. Titrate to an amber color that persists for 15 seconds after mixing. Not more than 1.0% of water is found.

Other requirements—It meets the requirements under *Sterility Tests* ⟨71⟩ and *Uniformity of Dosage Units* ⟨905⟩.

Assay—

Mobile phase—Add 1.03 g of sodium 1-heptanesulfonate to a mixture of 900 mL of water and 10 mL of methanol. Mix, then add sufficient glacial acetic acid and ammonium hydroxide, if necessary, to adjust the solution to a pH of 4.0. Add 50 mL of acetonitrile, then add water to make 1000 mL, and mix. Slight variation of the amount of acetonitrile may be required to improve resolution or adjust retention time. Degas the solution.

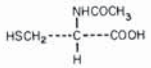
Standard preparation—Dissolve an accurately weighed quantity of USP Acetylcholine Chloride RS in *Mobile phase*, and dilute quantitatively and stepwise with *Mobile phase* to obtain a solution having a known concentration about equal to that of the acetylcholine chloride in the *Assay preparation*.

Assay preparation—Transfer the contents of 1 container of Acetylcholine Chloride for Ophthalmic Solution to a 10-mL volumetric flask with the aid of *Mobile phase*, add *Mobile phase* to volume, and mix.

Chromatographic system—Use a liquid chromatograph fitted with a 30-cm × 3.9-mm stainless steel column packed with packing L1, and a refractive index detector. The flow rate is about 2 mL per minute. Chromatograph replicate 50-µL injections of the *Standard preparation*, and record the peak response: the relative standard deviation is not more than 3.5%. Chromatograph a solution containing about 0.2% each of acetylcholine chloride and choline chloride: the resolution is not 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. Calculate the quantity, in mg, of $C_7H_{16}ClNO_2$ in the container taken by the formula $10C(r_U/r_S)$, in which C is the concentration, in mg per mL, of USP Acetylcholine Chloride RS in the *Standard preparation*, and r_U and r_S are the peak responses obtained from the *Assay preparation* and the *Standard preparation*, respectively.

Acetylcysteine



$C_5H_9NO_3S$ 163.19

L-Cysteine, *N*-acetyl-.

N-Acetyl-L-cysteine [*616-91-1*].

» Acetylcysteine contains not less than 98.0 percent and not more than 102.0 percent of $C_5H_9NO_3S$, calculated on the dried basis.

Packaging and storage—Preserve in tight containers.

Reference standard—*USP Acetylcysteine Reference Standard*—Dry at a pressure of about 50 mm of mercury at 70° for 4 hours before using.

Identification—The infrared absorption spectrum of a mineral oil dispersion of it, previously dried, exhibits maxima only at the same wavelengths as that of a similar preparation of USP Acetylcysteine RS.

Melting range, *Class I* ⟨741⟩: between 104° and 110°.

Specific rotation ⟨781⟩—In a 25-mL volumetric flask mix 1.25 g with 1 mL of disodium ethylene-diaminetetraacetate solution (1 in 100), add 7.5 mL of sodium hydroxide solution (1 in 25), and mix to dissolve. Dilute to volume with pH 7.0 buffer (prepared by mixing 29.5 mL of 1 *N* sodium hydroxide, 50 mL of 1 *M* monobasic potassium phosphate, and sufficient water to make 100 mL and, using a pH meter, adjusting to a pH of 7.0 ± 0.1 by adding, as necessary, more of either solution): the specific rotation, calculated on the dried basis, compared with a blank prepared with the same amounts of the same reagents, is between +21° and +27°.

pH ⟨791⟩: between 2.0 and 2.8, in a solution (1 in 100).

Loss on drying ⟨731⟩—Dry it at a pressure of about 50 mm of mercury at 70° for 4 hours: it loses not more than 1.0% of its weight.

Residue on ignition ⟨281⟩—Transfer to a tared fused silica dish about 2 g, weigh accurately, heat on a hot plate until thoroughly charred, cool, add 1 mL of sulfuric acid, and heat gently until fuming ceases. Ignite at 600° until the carbon is consumed. Not more than 0.5% is found.

Heavy metals, *Method II* ⟨231⟩—In a dropwise manner [*Caution—Exercise care, since explosion may occur*], wet the test specimen with 2 mL of nitric acid, and proceed as directed for the *Test Preparation:* the limit is 0.001%.

Assay—

Mobile phase—Dissolve 6.8 g of monobasic potassium phosphate in 1000 mL of water, filter through a membrane filter (0.45-µ porosity), and degas.

Internal standard solution—Dissolve about 1 g of *dl*-phenylalanine in 200 mL of freshly prepared sodium bisulfite solution (1 in 2000).

Standard preparation—Dissolve an accurately weighed quantity of USP Acetylcysteine RS in sodium bisulfite solution (1 in 2000) to obtain a solution having a known concentration of about 10 mg per mL. Pipet 10.0 mL of this solution and 10.0 mL of *Internal standard solution* into a 200-mL volumetric flask, dilute with sodium bisulfite solution (1 in 2000) to volume, and mix to obtain a *Standard preparation* having a known concentration of about 0.5 mg per mL.

Assay preparation—Transfer about 1000 mg of Acetylcysteine, accurately weighed, to a 100-mL volumetric flask. Dissolve in sodium bisulfite solution (1 in 2000), dilute with the same solvent to volume, and mix. Pipet 10.0 mL of this solution and 10.0 mL of *Internal standard solution* into a 200-mL volumetric flask, dilute with sodium bisulfite solution (1 in 2000) to volume, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 214-nm detector and a 3.9-mm × 30-cm column that contains packing L1. The flow rate is about 1.5 mL per minute. Chromatograph the *Standard preparation*, and record the peak responses as directed under *Procedure:* the relative standard deviation for replicate injections is not more than 2.0% and the resolution, R, factor between acetylcysteine and *dl*-phenylalanine is not less than 6.

Procedure—Separately inject equal volumes (about 5 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. The relative retention times are about 0.4 for acetylcysteine and 1.0 for *dl*-phenylalanine. Calculate the quantity, in mg, of $C_5H_9NO_3S$ in the Acetylcysteine taken by the formula $2000C(R_U/R_S)$, in which C is the concentration, in mg per mL, of USP Acetylcysteine RS in the *Standard preparation*, and R_U and R_S are the ratios of the peak response of acetylcysteine to that of *dl*-phenylalanine obtained from the *Assay preparation* and the *Standard preparation*, respectively.

Acetylcysteine Solution

» Acetylcysteine Solution is a sterile solution of Acetylcysteine in water, prepared with the aid of Sodium Hydroxide. It contains not less than 90.0 percent and not more than 110.0 percent of the labeled amount of $C_5H_9NO_3S$.

Packaging and storage—Preserve in single-dose or multiple-dose containers, preferably of Type I glass, tightly closed with a glass or polyethylene closure.

Reference standard—*USP Acetylcysteine Reference Standard*—Dry at a pressure of about 50 mm of mercury at 70° for 4 hours before using.

Identification—Place 2 mL in a 10-mL beaker, and adjust to a pH of about 3 (pH indicator paper) using 3 *N* hydrochloric acid. Add 500 mg to 1 g of finely powdered sodium chloride, in two portions of about 200 mg each initially, and then in smaller portions (about 25 mg), stirring after each addition, until a precipitate is formed. Allow to stand at room temperature for 15 minutes, and collect the residue by suction filtration. The acetylcysteine so obtained, after being dried as directed in the test for *Loss on drying* under

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