



INTERNATIONAL PHARMACOPOEIA MONOGRAPH ON ISONIAZID AND ETHAMBUTOL HYDROCHLORIDE TABLETS

REVISED DRAFT FOR COMMENTS

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ISONIAZID AND ETHAMBUTOL HYDROCHLORIDE TABLETS: Revised draft proposal for *The International Pharmacopoeia (October 2005)*

Note from the Secretariat: Certain editorial changes have been made to this revised draft text to conform to the style adopted for the 4th edition of the International Pharmacopoeia. For example, method texts have been assigned a number to avoid the need for page references.

Category. Antituberculosis drugs.

Storage. Isoniazid and Ethambutol hydrochloride tablets should be kept in tightly closed containers.

Additional information. Strength in the current WHO Model list of essential drugs:
150 mg Isoniazid and 400 mg Ethambutol hydrochloride.

Note from the Secretariat: Should information concerning tablet coating be included in this section?

Requirements

Complies with the monograph for “Tablets”.

Definition Isoniazid and Ethambutol hydrochloride tablets contain Isoniazid and Ethambutol hydrochloride. They contain not less than **90.0%** and not more than **110.0%** of the amounts of isoniazid ($C_6H_7N_3O$) and ethambutol hydrochloride ($C_{10}H_{24}N_2O_2, 2HCl$) stated on the label.

Identity tests

- Either test A or test B may be applied.
- A. See the test described below under “Assay”. The retention times of the two principal peaks in the chromatogram obtained with solution (1) correspond to those in the chromatogram obtained with solution (2).
- B. Carry out test B.1. or, where UV detection is not available, test B.2.

B.1 Carry out the test as described under 1.14.1 Thin-layer chromatography, using silica gel R6 as the coating substance and a mixture of 100 volumes of methanol R and 1.5 volumes of strong ammonia solution R as the mobile phase. Apply separately to the plate 5 μ l of each of the following two solutions in methanol R. For solution (A) shake a quantity of the powdered tablets equivalent to about 5 mg Isoniazid for 15 minutes with 5 ml of methanol R, filter, and use the filtrate. For solution (B) use 1 mg isoniazid RS and 2.67 mg ethambutol hydrochloride RS per ml of methanol R. After removing the plate from the chromatographic chamber, allow it to dry in a current of air and examine the chromatogram in ultraviolet light (254 nm).

The principal spots obtained with solution A correspond in position, appearance and intensity with those obtained with solution B.

B.2. Carry out the test as described under 1.14.1 Thin-layer chromatography, using silica gel R5 as the coating substance and a mixture of 100 volumes of methanol R and 1.5 volumes of strong ammonia solution R as the mobile phase. Apply separately to the plate 5 µl of each of the following two solutions in methanol R. For solution (A) shake a quantity of the powdered tablets equivalent to about 5 mg Isoniazid for 15 minutes with 5 ml of methanol R, filter, and use the filtrate. For solution (B) use 1 mg isoniazid RS and 2.67 mg ethambutol hydrochloride RS per ml of methanol R. After removing the plate from the chromatographic chamber, allow it to dry in a current of air, place in a chamber with iodine vapours, and allow to stand for 20 minutes. Examine the chromatogram immediately in daylight.

The principal spots obtained with solution A correspond in position, appearance and intensity with those obtained with solution B.

Assay

Determine by 1.14.4 High-performance liquid chromatography, using a stainless steel column (15 cm x 4.6 mm) packed with particles of silica gel, the surface of which has been modified with chemically bonded octadecylsilyl groups (5 µm)¹. As the mobile phase, use a solution prepared as follows: dissolve 50 g ammonium acetate R and 0.2 g copper(II) acetate R in 1000 ml of water and adjust to pH 5.0 with glacial acetic acid R. Mix 940 ml of this solution with 60 ml methanol R.

Prepare the following solutions in water. For solution (1) weigh and powder 20 tablets. Transfer a quantity of the powder equivalent to about 100 mg Ethambutol hydrochloride, accurately weighed, to a 500 ml volumetric flask. Dissolve in about 400 ml water by shaking for about 15 minutes. [If foaming occurs, use 400 ml of a 4% solution of methanol R in place of the water.] Dilute to 500 ml with water. Filter a portion of this solution through a 0.45 µm filter, discarding the first few ml of the filtered solution. For solution (2) dissolve 100 mg ethambutol hydrochloride RS and 37.5 mg isoniazid RS in 500 ml water.

Operate with a flow rate of 2.0 ml per minute. As a detector use an ultraviolet spectrophotometer set at a wavelength of about 270 nm.

Inject 20 µl of solution (2). The assay is not valid unless the resolution between the isoniazid peak, (the peak with the shorter retention time), and the ethambutol hydrochloride peak is at least 10.

Inject separately 20 µl of solution (2) in six replicate injections in the chromatographic system. The assay is not valid unless the relative standard deviation for peak areas of isoniazid and ethambutol hydrochloride, eluting in this order, is less than 2.0%.

Inject alternately 20 µl each of solutions (1) and (2).

Measure the areas of the peak responses obtained in the chromatograms from solutions (1) and (2), and calculate the content of isoniazid, C₆H₇N₃O and ethambutol hydrochloride, C₁₀H₂₄N₂O₂, 2HCl.

¹ Luna® is suitable

Dissolution test. To be added.

Draft for comments

A typical chromatogram of Isoniazid and Ethambutol hydrochloride.


