Norethindrone Acetate Tablets

Type of Posting: Revision Bulletin
Posting Date: 30–Sept–2016
Official Date: 01–Oct–2016
Expert Committee: Chemical Medicines Monographs 5
Reason for Revision: Compliance

In accordance with the Rules and Procedures of the 2015-2020 Council of Experts, the Chemical Medicines Monographs 5 Expert Committee has revised the Norethindrone Acetate Tablets monograph. The purpose for the revision is to add *Dissolution Test 2* for drug products approved by the FDA with different conditions and tolerances than the existing dissolution tests. This test was validated using a Phenomenex Hypersil ODS C18 brand of 4.6-mm x 25-cm, 5-µm packing L1 column. Additionally, minor editorial changes have been made to update the monograph to current USP style.

The Norethindrone Acetate Tablets Revision Bulletin supersedes the currently official Norethindrone Acetate Tablets monograph. The Revision Bulletin will be incorporated in the *First Supplement to USP 40–NF 35*.

Should you have any questions, please contact Ren-Hwa Yeh, Ph.D., Senior Scientific Liaison, (301–998–6818 or rhy@usp.org).
Norethindrone Acetate Tablets

DEFINITION
Norethindrone Acetate Tablets contain NLT 90.0% and NMT 110.0% of the labeled amount of norethindrone acetate (C22H28O3).

IDENTIFICATION
• A. INFRARED ABSORPTION (197K)
  Analysis: Mix an amount of powdered Tablets equivalent to 20 mg of norethindrone acetate to a separator, add 10 mL of water, and extract with three 25 mL portions of chloroform, filtering each extract through chloroform-washed cotton. Evaporate the combined chloroform extracts on a steam bath to dryness, reducing the heat as dryness is approached. Dissolve the residue in alcohol, transfer the solution to a 100-mL volumetric flask, dilute with alcohol to volume, and mix. Transfer a 5.0-mL aliquot to a 100-mL volumetric flask, and dilute with alcohol to volume.
  Acceptance criteria: The IR absorption spectrum of a potassium bromide dispersion prepared from the residue so obtained exhibits maxima only at the same wavelengths as that of a similar preparation of USP Norethindrone Acetate RS.

ASSAY
• Procedure
  Standard solution: 10 µg/mL of USP Norethindrone Acetate RS in alcohol
  Sample solution: Nominally 10 µg/mL of norethindrone acetate in alcohol prepared as follows. Transfer an amount of finely powdered Tablets (powder NLT 20 Tablets) equivalent to 20 mg of norethindrone acetate to a separator, add 10 mL of water, and extract with three 25 mL portions of chloroform, filtering each extract through chloroform-washed cotton. Evaporate the combined chloroform extracts on a steam bath to dryness, reducing the heat as dryness is approached. Dissolve the residue in alcohol, transfer the solution to a 100-mL volumetric flask, dilute with alcohol to volume, and mix. Transfer a 5.0-mL aliquot to a 100-mL volumetric flask, and dilute with alcohol to volume.
  Instrumental conditions
  Mode: UV
  Analytical wavelength: Maximum absorbance at about 248 nm
  Cell: 1 cm
  Blank: Alcohol
  Analysis
  Samples: Standard solution, Sample solution, and Blank
  Calculate the percentage of the labeled amount of norethindrone acetate (C22H28O3) in the portion of Tablets taken:
  \[
  \text{Result} = \left( \frac{A_U}{A_I} \right) \times \left( \frac{C_I}{C_U} \right) \times 100
  \]
  \[\begin{align*}
  A_U &= \text{absorbance of the Sample solution} \\
  A_I &= \text{absorbance of the Standard solution} \\
  C_I &= \text{concentration of the Standard solution (mg/mL)} \\
  C_U &= \text{nominal concentration of norethindrone acetate in the Sample solution (µg/mL)}
  \end{align*}\]

Acceptance criteria: 90.0%–110.0%

PERFORMANCE TESTS

Change to read:
• DISSOLUTION (711)
  Test 1: Dilute hydrochloric acid (1 in 100) containing 0.02% of sodium lauryl sulfate; 900 mL
  Apparatus 1: 100 rpm
  Time: 60 min
  Standard solution: A known concentration of USP Norethindrone Acetate RS in Medium. [NOTE—The Standard solution may be prepared by dissolving the Reference Standard in a volume of methanol, not exceeding 0.5% of the final volume of the solution, and diluting quantitatively with Medium.]
  Sample solution: Filter portions of the solution under test. Dilute with Medium if necessary.
  Instrumental conditions
  Mode: UV
  Analytical wavelength: Maximum absorbance at about 248 nm, measured from a baseline drawn from 350 to 310 nm and extending beyond the maximum peak.
  Analysis
  Samples: Standard solution and Sample solution
  Calculate the percentage of the labeled amount of norethindrone acetate (C22H28O3) dissolved:
  \[
  \text{Result} = \left( \frac{A_U}{A_I} \right) \times \left( \frac{C_I}{C_U} \right) \times D \times V \times 100
  \]
  \[\begin{align*}
  A_U &= \text{absorbance of the Sample solution} \\
  A_I &= \text{absorbance of the Standard solution} \\
  C_I &= \text{concentration of the Standard solution (mg/mL)} \\
  L &= \text{label claim (mg/Tablet)} \\
  D &= \text{dilution factor of the Sample solution} \\
  V &= \text{volume of Medium, 900 mL}
  \end{align*}\]
  Tolerances: NLT 70% (Q) of the labeled amount of norethindrone acetate (C22H28O3) is dissolved.
  Test 2: If the product complies with this test, the labeling indicates that it meets USP Dissolution Test 2.
  Medium: 0.2 g/L of sodium lauryl sulfate and 10 mL/L of hydrochloric acid in water; 900 mL
  Apparatus 1: 100 rpm
  Time: 30 min
  Mobile phase: Acetonitrile and water (60:40)
  Standard stock solution: 0.275 mg/mL of USP Norethindrone Acetate RS prepared as follows. Transfer an appropriate amount of USP Norethindrone Acetate RS to a suitable volumetric flask and dissolve in 50% of the flask volume of methanol. Sonicate to dissolve as needed. Dilute with Medium to volume.
  Standard solution: 0.0011 mg/mL of USP Norethindrone Acetate RS from the Standard stock solution prepared as follows. Transfer 2 mL of the Standard stock solution with Medium to 100 mL. Further dilute 5 mL of the resultant solution with Mobile phase to 25 mL. Pass a portion through a suitable filter paper.
  Sample solution: Pass a portion of the solution under test through a suitable filter. Dilute 5 mL of the filtrate with Mobile phase to 25 mL.
  Chromatographic system
  (See Chromatography (621), System Suitability.)
Mode: LC
Detector: UV 254 nm
Column: 4.6-mm × 25-cm; 5-µm packing L1
Injection volume: 100 µL
Run time: 1.5 times the retention time of norethindrone acetate

System suitability
Sample: Standard solution
Suitability requirements
Tailing factor: NMT 2.0
Relative standard deviation: NMT 2.0%

Analysis
Samples: Standard solution and Sample solution
Calculate the percentage of the labeled amount of norethindrone acetate (C22H28O3) dissolved:

Result = \( \left( \frac{r_s}{r_u} \right) \times C_s \times V \times (1/L) \times D \times 100 \)

- \( r_s \) = peak response of norethindrone acetate from the Sample solution
- \( r_u \) = peak response of norethindrone acetate from the Standard solution
- \( C_s \) = concentration of USP Norethindrone Acetate RS in the Standard solution (mg/mL)
- \( V \) = volume of Medium, 900 mL
- \( L \) = label claim (mg/Tablet)
- \( D \) = dilution factor of the Sample solution, 5

Tolerances: NLT 80% (Q) of the labeled amount of norethindrone acetate (C22H28O3) is dissolved.

ADDITIONAL REQUIREMENTS
- Packaging and Storage: Preserve in well-closed containers.

Add the following:

- 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 Norethindrone Acetate RS