Norethindrone Acetate Tablets

Type of Posting	Revision Bulletin
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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 ($C_{22}H_{28}O_3$).

IDENTIFICATION

• **A. INFRARED ABSORPTION ⟨197K⟩**

Analysis: Mix an amount of powdered Tablets equivalent to 50 mg of norethindrone with 15 mL of solvent hexane. Stir the solution occasionally for 15 min. Centrifuge the mixture, then decant and discard the solvent hexane. Extract the residue with two 10-mL portions of solvent hexane, centrifuging and decanting as before, and discard the solvent hexane. Add 25 mL of chloroform to the residue, mix by shaking for 1–2 min, and filter. Evaporate the filtrate to about 3 mL, add a few mL of solvent hexane to induce crystallization, and evaporate to dryness.

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 240 nm

Cell: 1 cm

Blank: Alcohol

Analysis

Samples: *Standard solution*, *Sample solution*, and *Blank*

Calculate the percentage of the labeled amount of norethindrone acetate ($C_{22}H_{28}O_3$) in the portion of Tablets taken:

$$\text{Result} = (A_U/A_S) \times (C_S/C_U) \times 100$$

A_U = absorbance of the *Sample solution*
A_S = absorbance of the *Standard solution*
C_S = concentration of USP Norethindrone Acetate RS in the *Standard solution* (µg/mL)
C_U = nominal concentration of norethindrone acetate in the *Sample solution* (µg/mL)

Acceptance criteria: 90.0%–110.0%

PERFORMANCE TESTS

Change to read:

• **DISSOLUTION ⟨711⟩**

•**Test 1**• (RB 1-Oct-2016)

Medium: 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 ($C_{22}H_{28}O_3$) dissolved:

•$\text{Result} = (A_U/A_S) \times (C_S/L) \times D \times V \times 100$• (RB 1-Oct-2016)

A_U = absorbance of the *Sample solution*
A_S = absorbance of the *Standard solution*
C_S = concentration of the *Standard solution* (mg/mL)
L = label claim (mg/Tablet)
D = dilution factor of the *Sample solution*
V = volume of *Medium*, 900 mL

Tolerances: NLT 70% (*Q*) of the labeled amount of norethindrone acetate ($C_{22}H_{28}O_3$) 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. Dilute 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
Flow rate: 1 mL/min
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 ($C_{22}H_{28}O_3$) dissolved:

$$\text{Result} = (r_U/r_S) \times C_S \times V \times (1/L) \times D \times 100$$

r_U = peak response of norethindrone acetate from the *Sample solution*
r_S = 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 ($C_{22}H_{28}O_3$) is dissolved.● (RB 1-Oct-2016)

- **UNIFORMITY OF DOSAGE UNITS ⟨905⟩,** *Content Uniformity*
Procedure for content uniformity
Standard solution: 10 µg/mL USP Norethindrone Acetate RS in alcohol
Sample solution: Nominally 10 µg/mL of norethindrone acetate prepared as follows. Transfer 1 finely powdered Tablet to a 100-mL volumetric flask with the aid of 75 mL of alcohol. Heat the alcohol to boiling, and allow the mixture to remain at a temperature just below the boiling point for 15 min, with occasional swirling. Cool to room temperature, dilute with alcohol to volume, and centrifuge a portion of the contents at 2000 rpm until the solution becomes clear. Dilute a portion of the supernatant with alcohol to obtain a final nominal concentration of 10 µg/mL of norethindrone acetate.
Instrumental conditions
Mode: UV
Analytical wavelength: Maximum absorbance at about 240 nm
Cell: 1 cm
Blank: Alcohol
Analysis
Samples: *Standard solution*, *Sample solution*, and *Blank*
Calculate the percentage of the labeled amount of norethindrone acetate ($C_{22}H_{28}O_3$) in the Tablet taken:

$$\text{Result} = (A_U/A_S) \times (C_S/C_U) \times 100$$

A_U = absorbance of the *Sample solution*
A_S = absorbance of the *Standard solution*
C_S = concentration of USP Norethindrone Acetate RS in the *Standard solution* (µg/mL)
C_U = nominal concentration of norethindrone acetate in the *Sample solution* from the Tablet, based on the labeled quantity/Tablet and the extent of dilution (µg/mL)
Acceptance criteria: Meet the requirements

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.● (RB 1-Oct-2016)
- **USP REFERENCE STANDARDS ⟨11⟩**
USP Norethindrone Acetate RS