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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

Delete the following:

▲• **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. ▲2S *(USP41)*

Add the following:

▲• **A.** The retention time of the major peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay*.▲2S *(USP41)*

Add the following:

▲• **B.** The UV spectrum of the major peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay*.▲2S *(USP41)*

ASSAY

Change to read:

• **Procedure**

▲**Solution A:** Water

Solution B: Acetonitrile

Mobile phase: See *Table 1*.

Table 1

Time (min)	Solution A (%)	Solution B (%)
0.0	60	40
4.0	60	40
40.0	40	60
50.0	10	90
55.0	10	90
56.0	60	40

Time (min)	Solution A (%)	Solution B (%)
60.0	60	40

Diluent: Methanol and water (60:40)

System suitability stock solution: 0.1 mg/mL each of USP Norethindrone Acetate RS, USP Norethindrone RS, and USP Norethindrone Related Compound B RS prepared as follows. Transfer the Reference Standards to a suitable volumetric flask. Add 50% of the final flask volume of acetonitrile to dissolve, and dilute with *Diluent* to volume.

System suitability solution: 0.05 mg/mL each of USP Norethindrone Acetate RS, USP Norethindrone RS, and USP Norethindrone Related Compound B RS in *Diluent* from *System suitability stock solution*

Standard solution: 0.1 mg/mL of USP Norethindrone Acetate RS in *Diluent*

Sample solution: Nominally 0.1 mg/mL of norethindrone acetate in *Diluent* prepared as follows. Transfer a quantity of finely powdered Tablets (NLT 20) equivalent to 20 mg of norethindrone acetate to a 20-mL volumetric flask. Add 15 mL of *Diluent* and sonicate for 30 min. Dilute with *Diluent* to volume. Centrifuge to obtain a clear supernatant. Transfer 5.0 mL of the supernatant to a 50-mL volumetric flask, and dilute with *Diluent* to volume.

Chromatographic system

(See *Chromatography ⟨621⟩, System Suitability*.)

Mode: LC

Detector: UV 254 nm. For *Identification B*, use a diode array detector in the range of 200–400 nm.

Column: 4.6-mm × 25-cm; 5-µm packing L7

Column temperature: 40°

Flow rate: 1.2 mL/min

Injection volume: 50 µL

System suitability

Samples: *System suitability solution* and *Standard solution*

[NOTE—See *Table 2* for relative retention times.]

Suitability requirements

Resolution: NLT 2.0 between norethindrone related compound B and norethindrone, *System suitability solution*

Tailing factor: NMT 1.5, *Standard solution*

Relative standard deviation: NMT 1.0%, *Standard solution*

Analysis

Samples: *Standard solution* and *Sample solution*

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

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times 100$$

r_U = peak response from the *Sample solution*

r_S = peak response from the *Standard solution*

C_S = concentration of USP Norethindrone Acetate RS in the *Standard solution* (mg/mL)

C_U = nominal concentration of norethindrone acetate in the *Sample solution* (mg/mL)

▲2S *(USP41)*

Acceptance criteria: 90.0%–110.0%

PERFORMANCE TESTS

• **DISSOLUTION ⟨711⟩**

Test 1

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:

$$\text{Result} = (A_U/A_S) \times (C_S/L) \times D \times V \times 100$$

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.

Change to read:

• **Uniformity of Dosage Units ⟨905⟩, *Content Uniformity*:** Meet the requirements

▲▲2S *(USP41)*

IMPURITIES

Add the following:

▲• **Organic Impurities**

Solution A, Solution B, Mobile phase, Diluent, and **System suitability solution:** Prepare as directed in the *Assay*.

Standard solution: 0.005 mg/mL of USP Norethindrone Acetate RS in *Diluent*

Sample solution: Nominally 1.0 mg/mL of norethindrone acetate in *Diluent* prepared as follows. Transfer a quantity of finely powdered Tablets (NLT 20) equivalent to 20 mg of norethindrone acetate to a 20-mL volumetric flask. Add 15 mL of *Diluent* and sonicate for 30 min. Dilute with *Diluent* to volume. Centrifuge to obtain a clear supernatant. Use the supernatant.

Chromatographic system

(See *Chromatography ⟨621⟩, System Suitability*.)

Mode: LC

Detector: UV 210 nm for norethindrone acetate 5(10)-ene isomer; UV 254 nm for all other impurities

Column: 4.6-mm × 25-cm; 5-µm packing L7

Column temperature: 40°

Flow rate: 1.2 mL/min

Injection volume: 50 µL

System suitability

Samples: *System suitability solution* and *Standard solution*

[Note—See *Table 2* for relative retention times.]

Suitability requirements

Resolution: NLT 2.0 between norethindrone and norethindrone related compound B, *System suitability solution*

Relative standard deviation: NMT 5.0%, *Standard solution*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of norethindrone acetate 5(10)-ene isomer (detected at UV 210 nm) in the portion of Tablets taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times (1/F) \times 100$$

r_U = peak response of norethindrone acetate 5(10)-ene isomer 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)

C_U = nominal concentration of norethindrone acetate in the *Sample solution* (mg/mL)

F = relative response factor (see *Table 2*)

Calculate the percentage of each specified or unspecified degradation product (detected at UV 254 nm) in the portion of Tablets taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times (1/F) \times 100$$

r_U = peak response of each specified or unspecified degradation product 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)

C_U = nominal concentration of norethindrone acetate in the *Sample solution* (mg/mL)

F = relative response factor (see *Table 2*)

Acceptance criteria: See *Table 2*. The reporting threshold is 0.1%.

Table 2

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
6β-Hydroxynorethindrone acetate[a,b]	0.34	0.53	—
Norethindrone related compound B[b]	0.46	1.0	—
Norethindrone	0.51	1.0	0.5
6-Keto norethindrone acetate[c]	0.59	0.73	0.5
6β-Acetylnorethindrone acetate[b,d]	0.67	1.0	—
17-Acetyl norethindrone acetate analog[b,e]	0.82	1.0	—
Norethindrone acetate	1.00	1.0	—
Destrimethylene quingestanol acetate[b,f]	1.63	1.0	—
Desethylene quingestanol acetate[b,g]	1.67	1.0	—
Norethindrone acetate 5-ene isomer[b,h]	1.09	0.57	—
Norethindrone acetate 5(10)-ene isomer[i]	1.15	0.73	0.5
Any individual degradation product	—	1.0	0.5
Total impurities	—	—	2.0

[a] 6β-Hydroxy-3-oxo-19-nor-17α-pregn-4-en-20-yn-17-yl acetate.

[b] Process impurity included in the table for identification only. Process impurities are controlled in the drug substance and are not to be reported or included in the total impurities of the drug product.

[c] 3,6-Dioxo-19-nor-17α-pregn-4-en-20-yn-17-yl acetate.

[d] 6β-Acetyl-3-oxo-19-nor-17α-pregn-4-en-20-yn-17-yl acetate.

[e] 3,20-Dioxo-19-nor-17α-pregn-4-en-17-yl acetate.

[f] 3-Ethoxy-19-nor-17βα-pregn-3,5-dien-20-yn-17-yl acetate.

[g] 3-Isopropoxy-19-nor-17βα-pregn-3,5-dien-20-yn-17-yl acetate.

[h] 3-Oxo-19-nor-17α-pregn-5-en-20-yn-17-yl acetate.

[i] 3-Oxo-19-nor-17α-pregn-5(10)-en-20-yn-17-yl acetate.

▲2S *(USP41)*

ADDITIONAL REQUIREMENTS

Change to read:

• **Packaging and Storage:** Preserve in well-closed containers. ▲Store at controlled room temperature.▲2S *(USP41)*

• **Labeling:** When more than one *Dissolution* test is given, the labeling states the *Dissolution* test used only if *Test 1* is not used.

Change to read:

• **USP Reference Standards** ⟨11⟩

▲ USP Norethindrone RS▲2S *(USP41)*

USP Norethindrone Acetate RS

▲ USP Norethindrone Related Compound B RS

Estr-4-ene-3,17-dione.

$C_{18}H_{24}O_2$ 272.39▲2S *(USP41)*

Auxiliary Information - Please check for your question in the FAQs before contacting USP.

Topic/Question	Contact	Expert Committee
NORETHINDRONE ACETATE TABLETS	Documentary Standards Support	SM52020 Small Molecules 5
REFERENCE STANDARD SUPPORT	RS Technical Services RSTECH@usp.org	SM52020 Small Molecules 5

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