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Norethindrone Acetate and Ethinyl Estradiol Tablets

DEFINITION

Norethindrone Acetate and Ethinyl Estradiol Tablets contain NLT 90.0% and NMT 110.0% of the labeled amount of norethindrone acetate ($C_{22}H_{28}O_3$), and NLT 88.0% and NMT 112.0% of the labeled amount of ethinyl estradiol ($C_{20}H_{24}O_2$).

IDENTIFICATION

- **A.** The retention times of the major peaks of the *Sample solution* correspond to those of the *Standard solution*, as obtained in the *Assay*.
- **B.** The UV spectra of the major peaks of the *Sample solution* correspond to those of the *Standard solution*, as obtained in the *Assay*.

ASSAY

- **Procedure**

Mobile phase: Acetonitrile, methanol, and water (40:5:55)

Diluent: Acetonitrile and water (50:50)

Standard solution: 0.090 mg/mL of USP Norethindrone Acetate RS and 1.76 µg/mL of USP Ethinyl Estradiol RS in *Diluent*

Sample solution: Nominally 0.1 mg/mL of norethindrone acetate from Tablets prepared as follows. Transfer an appropriate number of Tablets (NLT 20) to a volumetric flask. Fill the flask with *Diluent* to about 75% of volume, and disintegrate the Tablets by mechanical shaking and sonication. Allow the solution to equilibrate to room temperature, and dilute with *Diluent* to volume. Centrifuge a portion of the solution using glass centrifuge tubes, and use the clear supernatant.

Chromatographic system

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

Mode: LC

Detector: UV 200 nm. For *Identification B*, use a diode array detector in the range of 200–600 nm.

Column: 4.6-mm × 15-cm; 5-µm packing L1

Flow rate: 1.5 mL/min

Injection volume: 100 µL

Run time: NLT 1.2 times the retention time of norethindrone acetate

System suitability

Sample: *Standard solution*

[Note—The relative retention times for ethinyl estradiol and norethindrone acetate are about 0.28 and 1.0, respectively.]

Suitability requirements

Resolution: NLT 10.0 between ethinyl estradiol and norethindrone acetate

Tailing factor: NMT 2.0 for ethinyl estradiol and norethindrone acetate

Relative standard deviation: NMT 2.0% for ethinyl estradiol and norethindrone acetate

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of norethindrone acetate ($C_{22}H_{28}O_3$) and ethinyl estradiol ($C_{20}H_{24}O_2$) in the portion of Tablets taken:

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

r_U = peak response of norethindrone acetate or ethinyl estradiol from the *Sample solution*

r_S = peak response of norethindrone acetate or ethinyl estradiol from the *Standard solution*

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

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

Acceptance criteria

Norethindrone acetate: 90.0%–110.0%

Ethinyl estradiol: 88.0%–112.0%

PERFORMANCE TESTS

Change to read:

• **Dissolution** ⟨711⟩

Test 1

0.025 M acetate buffer solution: Transfer 5.22 g of anhydrous sodium acetate and 2.2 g of glacial acetic acid to a 4-L volumetric flask, add 3.5 L of water, and adjust with 1 N sodium hydroxide to a pH of 5.0. Dilute with water to volume.

Medium: *0.025M acetate buffer solution* with 0.15% sodium lauryl sulfate, prepared as follows. Weigh 6 g of sodium lauryl sulfate into a 4-L volumetric flask, add 1.5 L of *0.025 M acetate buffer solution*, mix, and dilute with *0.025 M acetate buffer solution* to volume; 600 mL.

Apparatus 2: 75 rpm

Time: 60 min

Mobile phase: Acetonitrile, tetrahydrofuran, and 0.2% phosphoric acid (38:8:54)

Standard solution: USP Norethindrone Acetate RS and USP Ethinyl Estradiol RS dissolved in a minimum amount of acetonitrile, and diluted with *Medium* to obtain a solution having known concentrations equivalent to the expected concentrations of the solution under test

Sample solution: Withdraw a 2-mL aliquot of the solution under test, using a glass pipet or syringe, and centrifuge. Use the supernatant. [Note—The use of a centrifuge speed of 2000 rpm for 5 min may be suitable.]

Chromatographic system

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

Mode: LC

Detectors

Detector 1: UV 242 nm for norethindrone acetate

Detector 2: Fluorescence with an excitation wavelength set at 210 nm and an emission wavelength set at 310 nm for ethinyl estradiol

Columns

Guard: 4-mm × 1.25-cm; 5-µm packing L1

Analytical: 6-mm × 4-cm; 3-µm packing L1

Flow rate: 1 mL/min

Injection volume: 200 µL

System suitability

Sample: *Standard solution*

Suitability requirements

Tailing factor: NMT 2.0 for norethindrone acetate and ethinyl estradiol

Relative standard deviation: NMT 2.5% for norethindrone acetate and ethinyl estradiol

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of norethindrone acetate ($C_{22}H_{28}O_3$) or ethinyl estradiol ($C_{20}H_{24}O_2$) dissolved:

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

r_U = peak response of norethindrone acetate or ethinyl estradiol from the *Sample solution*

r_S = peak response of norethindrone acetate or ethinyl estradiol from the *Standard solution*

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

V = volume of *Medium*, 600 mL

L = label claim of norethindrone acetate (mg/Tablet) or ethinyl estradiol (µg/Tablet)

Tolerances: NLT 80% (Q) of the labeled amounts of norethindrone acetate ($C_{22}H_{28}O_3$) and ethinyl estradiol ($C_{20}H_{24}O_2$) are dissolved.

Test 2: If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 2*.

Medium: Prepare *Medium* as directed in *Test 1*; 600 mL

0.2% phosphoric acid solution: To a suitable volumetric flask add water to about 50% of the flask volume and phosphoric acid equivalent to 0.2% of the flask volume. Dilute with water to volume and mix.

Apparatus 2: 75 rpm

Time: 30 min

Mobile phase: Acetonitrile, tetrahydrofuran, and *0.2% phosphoric acid solution* (515:55:470)

Standard stock solution A: 0.0165 mg/mL of USP Norethindrone Acetate RS in acetonitrile. Sonicate to dissolve.

Standard stock solution B: 1.08 µg/mL of USP Ethinyl Estradiol RS in acetonitrile. Sonicate to dissolve.

Standard solution: 0.00165 mg/mL of USP Norethindrone Acetate RS and 0.0324 µg/mL of USP Ethinyl Estradiol RS in *Medium* from *Standard stock solution A* and *Standard stock solution B* prepared as follows. Pipette 10.0 mL of *Standard stock solution A* and 3.0 mL of *Standard stock solution B* into a 100-mL volumetric flask. Dilute with *Medium* to volume.

Sample solution: Centrifuge a portion of the solution under test. Use the supernatant.

[NOTE—The use of a centrifuge speed of 3000 rpm for 5 min may be suitable.]

Chromatographic system

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

Mode: LC

Detectors

Detector 1: UV 242 nm for norethindrone acetate

Detector 2: Fluorescence with an excitation wavelength set at 285 nm and an emission wavelength set at 310 nm for ethinyl estradiol

Column: 4.6-mm x 15-cm; 5-µm packing L1

Flow rate: 1 mL/min

Injection volume: 200 µL

Run time: NLT 1.5 times the retention time of norethindrone acetate

System suitability

Sample: *Standard solution*

[NOTE—The relative retention times for ethinyl estradiol and norethindrone acetate are 0.6 and 1.0, respectively.]

Suitability requirements

Tailing factor: NMT 2.0 for norethindrone acetate and ethinyl estradiol

Relative standard deviation: NMT 2.5% for norethindrone acetate and ethinyl estradiol

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of norethindrone acetate ($C_{22}H_{28}O_3$) or ethinyl estradiol ($C_{20}H_{24}O_2$) dissolved:

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

r_U = peak response of norethindrone acetate or ethinyl estradiol from the *Sample solution*

r_S = peak response of norethindrone acetate or ethinyl estradiol from the *Standard* solution

C_S = concentration of USP Norethindrone Acetate RS (mg/mL) or USP Ethinyl Estradiol RS (▲µg▲ (ERR 1-Apr-2023) /mL) in the *Standard solution*

V = volume of *Medium*, 600 mL

L = label claim of norethindrone acetate (mg/Tablet) or ethinyl estradiol (µg/Tablet)

Tolerances: NLT 80% (*Q*) of the labeled amounts of norethindrone acetate ($C_{22}H_{28}O_3$) and ethinyl estradiol ($C_{20}H_{24}O_2$) are dissolved.

• **UNIFORMITY OF DOSAGE UNITS ⟨905⟩:** Meet the requirements

ADDITIONAL REQUIREMENTS

• **PACKAGING AND STORAGE:** Preserve in well-closed containers. Store at controlled room temperature.

• **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 Ethinyl Estradiol RS

USP Norethindrone Acetate RS

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

Topic/Question	Contact	Expert Committee
NORETHINDRONE ACETATE AND ETHINYL ESTRADIOL TABLETS	Documentary Standards Support	SM52020 Small Molecules 5

Topic/Question	Contact	Expert Committee
REFERENCE STANDARD SUPPORT	RS Technical Services RSTECH@usp.org	SM52020 Small Molecules 5

Chromatographic Database Information: Chromatographic Database

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