Drospirenone and Ethinyl Estradiol Tablets

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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 Drospirenone and Ethinyl Estradiol Tablets monograph.

The purpose of this revision is to:

- Widen the limit for 6-keto ethinyl estradiol in *Table 2* from NMT 0.5% to NMT 0.8% in the *Acceptance Criteria* for drug products labeled to contain 3 mg of drospirenone and 0.02 mg of ethinyl estradiol to accommodate the sponsor's FDA-approved specification.

- Widen the limit for any unspecified degradation product in *Table 2* from NMT 0.3% to NMT 0.4% in the *Acceptance Criteria* for drug products labeled to contain 3 mg of drospirenone and 0.03 mg of ethinyl estradiol to accommodate the sponsor's FDA-approved specification.

The Drospirenone and Ethinyl Estradiol Tablets Revision Bulletin supersedes the currently official monograph.

Should you have any questions, please contact Mary Koleck, Senior Scientific Liaison (301-230-7420 or mpk@usp.org).

Drospirenone and Ethinyl Estradiol Tablets

DEFINITION

Drospirenone and Ethinyl Estradiol Tablets contain NLT 90.0% and NMT 110.0% of the labeled amount of drospirenone ($C_{24}H_{30}O_3$) and NLT 90.0% and NMT 110.0% of the labeled amount of ethinyl estradiol ($C_{20}H_{24}O_2$).

IDENTIFICATION

• **A.** The retention times of the drospirenone and ethinyl estradiol peaks of the *Sample solution* correspond to those of the *Standard solution*, as obtained in the *Assay*.

ASSAY

• **PROCEDURE**

Solution A: Dissolve 132 g of dibasic ammonium phosphate in 0.8 L of water, adjust with phosphoric acid to a pH of 6.8, and dilute to 1 L.

Solution B: *Solution A* and water (1:24)

Mobile phase: Acetonitrile and *Solution B* (1:1). Adjust with phosphoric acid to a pH of 6.8.

Standard solution: (*L*/25) mg/mL of USP Drospirenone RS and USP Ethinyl Estradiol RS in *Mobile phase*, where *L* is the Tablet label claim, in mg/Tablet, of each compound

Sample solution: Transfer 10 Tablets to a 250-mL volumetric flask, add 230 mL of *Mobile phase*, and sonicate with intermittent shaking for NLT 10 min, or until the Tablets are completely dispersed. Equilibrate to room temperature. Dilute with *Mobile phase* to volume, and centrifuge the sample until a clear supernatant is obtained. Use the supernatant.

Chromatographic system

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

Mode: LC

Detector 1: UV 270 nm for drospirenone

Detector 2: Fluorescence, excitation wavelength at 285 nm, emission wavelength at 315 nm for ethinyl estradiol. [NOTE—*Detector 1* and *Detector 2* are connected in series.]

Column: 4.0-mm × 12.5-cm; 3-µm packing L1

Column temperature: 25 ± 3°

Flow rate: 1.2 mL/min

Injection volume: 20 µL

System suitability

Sample: *Standard solution*

Suitability requirements

Tailing factor: Between 0.8 and 1.8 for both drospirenone and ethinyl estradiol

Relative standard deviation: NMT 2.0% for both drospirenone and ethinyl estradiol

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of drospirenone ($C_{24}H_{30}O_3$) in the portion of Tablets taken:

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

r_U = peak response of drospirenone from the *Sample solution*

r_S = peak response of drospirenone from the *Standard solution*

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

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

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of 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 ethinyl estradiol from the *Sample solution*

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

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

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

Acceptance criteria: 90.0%–110.0% of ethinyl estradiol; 90.0%–110.0% of drospirenone

PERFORMANCE TESTS

• **DISSOLUTION** ⟨711⟩

Test 1: For drug products labeled to contain 3 mg of drospirenone and 0.03 mg of ethinyl estradiol, or 3 mg of drospirenone and 0.02 mg of ethinyl estradiol

Medium: Water; 900 mL

Apparatus 2: 50 rpm

Time: 30 min

Standard solution: (*L*/900) mg/mL of USP Drospirenone RS and USP Ethinyl Estradiol RS in *Medium*, where *L* is the Tablet label claim of each compound. A volume of methanol not exceeding 2% of the final total volume of solution may be used to aid in dissolving these compounds.

Sample solution: Pass a portion of the solution under test through a suitable cellulose filter of 0.45-µm pore size, discarding the first 10 mL.

Mobile phase: Acetonitrile and water (40:60)

Chromatographic system

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

Mode: LC

Detector: UV 270 nm (for drospirenone), in series with a fluorescence detector (for ethinyl estradiol), with excitation at 210 nm and detection at 315 nm, or with excitation at 281 nm and detection at 305 nm

Column: 4.6-mm × 6-cm; 3-µm packing L1

Column temperature: 22°

Flow rate: 1 mL/min

Injection volume: 100 µL

System suitability

Sample: *Standard solution*

Suitability requirements

Column efficiency: NLT 2000 for both drospirenone and ethinyl estradiol

Tailing factor: Between 0.8 and 1.5 for both drospirenone and ethinyl estradiol

Relative standard deviation: NMT 3% for both drospirenone and ethinyl estradiol

Samples: *Standard solution* and *Sample solution*

[NOTE—In *Medium*, drospirenone is partially converted into 17-epidrospirenone, which has a relative retention time of approximately 1.2 relative to drospirenone. The amount of drospirenone dissolved is calculated from the sum of drospirenone and 17-epidrospirenone.]

Calculate the percentage of the labeled amounts of drospirenone ($C_{24}H_{30}O_3$) and ethinyl estradiol ($C_{20}H_{24}O_2$) dissolved:

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

r_U = peak response from the *Sample solution*

r_S = peak response from the *Standard solution*

C_S = concentration of the *Standard solution* (mg/mL)
L = label claim (mg/Tablet)
V = volume of *Medium*, 900 mL

Tolerances: NLT 85% (*Q*) of the labeled amount of drospirenone and NLT 75% (*Q*) of the labeled amount of ethinyl estradiol is dissolved.

Test 2: For drug products labeled to contain 3 mg of drospirenone and 0.02 mg of ethinyl estradiol. If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 2*.
Medium: Water; 900 mL
Apparatus 2: 50 rpm
Time: 30 min
Standard solution: (*L*/900) mg/mL of USP Drospirenone RS and USP Ethinyl Estradiol RS in *Medium*, where *L* is the Tablet label claim of each compound
Sample solution: Centrifuge a portion of the solution under test at 3500 rpm for 15 min, and use the supernatant.
Mobile phase: Acetonitrile, methanol, and water (40:5:55)
Chromatographic system
(See *Chromatography* ⟨621⟩*, System Suitability*.)
Mode: LC
Detector: UV 260 nm (for drospirenone), in series with a fluorescence detector (for ethinyl estradiol), with excitation at 280 nm and detection at 310 nm
Column: 4.6-mm × 10-cm; 3-µm packing L1
Temperatures
Column: 30°
Autosampler: 5°
Flow rate: 1 mL/min
Injection volume: 200 µL
System suitability
Sample: *Standard solution*
Suitability requirements
Tailing factor: NMT 2 for both drospirenone and ethinyl estradiol
Relative standard deviation: NMT 3% for both drospirenone and ethinyl estradiol
Samples: *Standard solution* and *Sample solution*
Calculate the percentage of the labeled amounts of drospirenone ($C_{24}H_{30}O_3$) and ethinyl estradiol ($C_{20}H_{24}O_2$) dissolved:

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

r_U = peak response from the *Sample solution*
r_S = peak response from the *Standard solution*
C_S = concentration of the *Standard solution* (mg/mL)
L = label claim (mg/Tablet)
V = volume of *Medium*, 900 mL

Tolerances: NLT 80% (*Q*) of the labeled amount of drospirenone and NLT 85% (*Q*) of the labeled amount of ethinyl estradiol is dissolved.

Test 3: For drug products labeled to contain 3 mg of drospirenone and 0.03 mg of ethinyl estradiol, or 3 mg of drospirenone and 0.02 mg of ethinyl estradiol. If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 3*.
Medium: Water; 900 mL
Apparatus 2: 50 rpm
Time: 30 min
Mobile phase: Acetonitrile and water (50:50)
Standard stock solution A: 2.8 µg/mL of USP Ethinyl Estradiol RS in acetonitrile. Sonicate as needed.
Standard stock solution B: 168 µg/mL of USP Drospirenone RS in acetonitrile. Sonicate as needed.
Standard solution: (*L*/900) mg/mL of USP Drospirenone RS and USP Ethinyl Estradiol RS in *Medium* from *Standard stock solution A* and *Standard stock solution B*, where *L* is the Tablet label claim of each compound.
Sample solution: Pass a portion of the solution under test through a suitable glass filter of 1-µm pore size, discarding the first 5 mL.
Chromatographic system
(See *Chromatography* ⟨621⟩*, System Suitability*.)
Mode: LC
Detector: UV 265 nm (for drospirenone), in series with a fluorescence detector (for ethinyl estradiol), with excitation at 285 nm and detection at 310 nm
Column: 4.6-mm × 15-cm; 5-µm packing L11
Temperatures
Column: 30°
Autosampler: 10°
Flow rate: 1 mL/min
Injection volume: 50 µL
System suitability
Sample: *Standard solution*
Suitability requirements
Tailing factor: NMT 2.0 for both drospirenone and ethinyl estradiol
Relative standard deviation: NMT 2.0% for both drospirenone and ethinyl estradiol
Samples: *Standard solution* and *Sample solution*
Calculate the percentage of the labeled amounts of drospirenone ($C_{24}H_{30}O_3$) and 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 from the *Sample solution*
r_S = peak response from the *Standard solution*
C_S = concentration of the *Standard solution* (mg/mL)
V = volume of *Medium*, 900 mL
L = label claim (mg/Tablet)

Tolerances: NLT 80% (*Q*) of the labeled amount of drospirenone and NLT 75% (*Q*) of the labeled amount of ethinyl estradiol is dissolved.

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

IMPURITIES

Change to read:

• **Organic Impurities**
Solution A: Acetonitrile, methanol, and water (26:19:55)
Solution B: Acetonitrile, methanol, and water (76:19:5)
Mobile phase: See *Table 1*.

Table 1

Time (min)	Flow (mL/min)	Solution A (%)	Solution B (%)
0	0.5	90	10
40	0.5	90	10
53	0.5	0	100
59	1.0	0	100
60	0.5	90	10

Table 1 *(continued)*

Time (min)	Flow (mL/min)	Solution A (%)	Solution B (%)
70	0.5	90	10

System suitability stock solution: (L_1 × 18/100) µg/mL of USP Drospirenone RS in *Solution A*, where L_1 is the label claim (µg/Tablet) of drospirenone

System suitability solution: Transfer 1.0 mL of the *System suitability stock solution* into a 10-mL volumetric flask, add 1.0 mL of 0.1 N hydrochloric acid, and heat for 30 min in a 40° water bath. Immediately add 1 mL of 0.1 N sodium hydroxide (NaOH) and allow to reach room temperature. Dilute with *Solution A* to volume to obtain a solution containing drospirenone and 17-epidrospirenone. [NOTE—Sodium hydroxide (NaOH) must be added immediately after heating for the reaction to proceed properly. The drospirenone to 17-epidrospirenone ratio must be between 3:1 and 7:1.]

Standard solution: (L_1 × 15/1000) µg/mL of USP Drospirenone RS, (L_2 × 30/1000) µg/mL of USP Ethinyl Estradiol RS, and (L_2 × 30/1000) µg/mL of USP Ethinyl Estradiol Related Compound B RS in *Solution A*, where L_1 and L_2 are the label claim (µg/Tablet) of drospirenone and ethinyl estradiol, respectively

Sensitivity solution: (L_1 × 15/10,000) µg/mL of USP Drospirenone RS, (L_2 × 30/10,000) µg/mL of USP Ethinyl Estradiol RS, and (L_2 × 30/10,000) µg/mL of USP Ethinyl Estradiol Related Compound B RS in *Solution A*, where L_1 and L_2 are the label claim (µg/Tablet) of drospirenone and ethinyl estradiol, respectively, prepared from the *Standard solution*

Sample solution: Transfer 15 Tablets to a 10-mL glass-stoppered test tube, and add 5.0 mL of *Solution A*. Shake vigorously, sonicate for NLT 5 min, and place in an ice bath for NLT 10 min. Centrifuge the sample at least until an almost clear supernatant is obtained. Filter the supernatant, and use the filtrate.

Chromatographic system
(See *Chromatography* ⟨621⟩*, System Suitability*.)
Mode: LC
Detector 1: UV 222 nm
Detector 2: Fluorescence, excitation wavelength at 215 nm, emission wavelength at 315 nm. Monitor the signal at 344 nm for ethinyl estradiol related compound B (typically between 37 and 42 min). [NOTE—*Detector 1* and *Detector 2* are connected in series. Use the response at 344 nm to quantify ethinyl estradiol related compound B.]
Column: 3.0-mm × 30-cm; 3-µm packing L1 followed, in series, by a 4.6-mm × 10-cm; chromolith packing L1
Column temperature: 40°
Flow rate: See *Table 1*.
Injection volume: 20 µL

System suitability
Samples: *System suitability solution*, *Standard solution*, and *Sensitivity solution*
Suitability requirements
Tailing factor: Between 0.8 and 1.5 for both drospirenone and ethinyl estradiol, *Standard solution*
Resolution: NLT 2.0 between drospirenone and 17-epidrospirenone, *System suitability solution*
Relative standard deviation: NMT 5.0% for both drospirenone and ethinyl estradiol, *Standard solution*
Signal-to-noise ratio: NLT 10 for drospirenone and ethinyl estradiol related compound B and NLT 7.0 for ethinyl estradiol, *Sensitivity solution*

Analysis
Samples: *Standard solution* and *Sample solution*
Identify the ethinyl estradiol degradation products using the relative retention times given in *Table 2*.
Calculate the percentage of each ethinyl estradiol degradation product and unspecified degradation products 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 ethinyl estradiol degradation product from the *Sample solution*
r_S = peak response of ethinyl estradiol from the *Standard solution*
C_S = concentration of USP Ethinyl Estradiol RS in the *Standard solution* (µg/mL)
C_U = nominal concentration of ethinyl estradiol in the *Sample solution* (µg/mL)
F = relative response factor for each degradation product (see *Table 2*)

Samples: *Standard solution* and *Sample solution*
Calculate the percentage of ethinyl estradiol related compound B in the portion of Tablets taken:

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

r_U = peak response of ethinyl estradiol related compound B from the *Sample solution*
r_S = peak response of ethinyl estradiol related compound B from the *Standard solution*
C_S = concentration of USP Ethinyl Estradiol Related Compound B RS in the *Standard solution* (µg/mL)
C_U = nominal concentration of ethinyl estradiol in the *Sample solution* (µg/mL)

Samples: *Standard solution* and *Sample solution*
Identify the drospirenone degradation products using the relative retention times given in *Table 3*.
Calculate the percentage of each drospirenone degradation product 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 drospirenone degradation product from the *Sample solution*
r_S = peak response of drospirenone from the *Standard solution*
C_S = concentration of USP Drospirenone RS in the *Standard solution* (µg/mL)
C_U = nominal concentration of drospirenone in the *Sample solution* (µg/mL)
F = relative response factor for each degradation product (see *Table 3*)

Acceptance criteria [NOTE—Report only degradation products greater than 0.1%.]
Individual degradation products: See *Table 2* for ethinyl estradiol and *Table 3* for drospirenone.
Total degradation products: NMT 3.5%

ADDITIONAL REQUIREMENTS

- **PACKAGING AND STORAGE:** Preserve in well-closed containers.
- **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 Drospirenone RS

Table 2

Name	Detection Mode	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)[a]	Acceptance Criteria, NMT (%)[b]
6α-Hydroxy ethinyl estradiol[c]	Fl (215 nm/315 nm)[g]	0.25	0.73	0.8	0.8
6β-Hydroxy ethinyl estradiol[d]	Fl (215 nm/315 nm)	0.27	0.64	0.8	0.8
6-Keto ethinyl estradiol[e]	UV 222 nm	0.41	2.3	1.5	▲0.8▲ (RB 1-Apr-2019)
Ethinyl estradiol related compound B[f]	Fl (215 nm/344 nm)	0.88	—	1.0	1.0
Ethinyl estradiol	Fl (215 nm/315 nm)	1.0	—	—	—
Any unspecified degradation product	Fl (215 nm/315 nm) and UV 222[h]	—	1.0	▲0.4▲ (RB 1-Apr-2019)	0.5
Total degradation product	—	—	—	3.0	2.5

[a] Limits for drug products labeled to contain 3 mg of drospirenone and 0.03 mg of ethinyl estradiol.
[b] Limits for drug products labeled to contain 3 mg of drospirenone and 0.02 mg of ethinyl estradiol.
[c] 19-Nor-6α,17α-pregna-1,3,5(10)-trien-20-yne-3,6,17-triol.
[d] 19-Nor-6β,17α-pregna-1,3,5(10)-trien-20-yne-3,6,17-triol.
[e] 19-Nor-17α-pregna-1,3,5(10)-trien-20-yne-3,17-diol-6-one.
[f] Δ9,11-Ethinyl estradiol. 19-Nor-17α-pregna-1,3,5(10),9(11)-tetraen-20-yne-3,17-diol.
[g] Fl = Fluorescence.
[h] Determine unknown impurities using both modes of detection. Report the values from the detection mode that yield higher impurity levels.

Table 3

Name	Detection Mode (λ nm)	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)[a]	Acceptance Criteria, NMT (%)[b]
Drospirenone	UV 222	0.75	—	—	—
17-Epidrospirenone[c]	UV 222	0.83	1.0	0.3	0.3
Ethinyl estradiol	UV 222	1.0	—	—	—
Any unspecified degradation product	UV 222	—	1.0	0.3	0.5
Total degradation product	—	—	—	0.5	1.0

[a] Limits for drug products labeled to contain 3 mg of drospirenone and 0.03 mg of ethinyl estradiol.
[b] Limits for drug products labeled to contain 3 mg of drospirenone and 0.02 mg of ethinyl estradiol.
[c] 17-Hydroxy-6β,7β:15β,16β-dimethylene-3-oxo-17β-pregn-4-ene-21-carboxylic acid, γ-lactone.

USP Ethinyl Estradiol RS
USP Ethinyl Estradiol Related Compound B RS
19-Nor-17α-pregna-1,3,5(10),9(11)-tetraen-20-yne-3,17-diol monohydrate.
$C_{20}H_{22}O_2 \cdot H_2O$ 312.40