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Nevirapine Oral Suspension

DEFINITION
Nevirapine Oral Suspension contains NLT 90.0% and NMT 110.0% of the labeled amount of nevirapine ($C_{15}H_{14}N_4O$).

IDENTIFICATION

• **A. Thin-Layer Chromatography** ⟨201⟩

Standard solution: 5 mg/mL of USP Nevirapine Anhydrous RS in chloroform

Sample solution: Transfer a volume of Oral Suspension, equivalent to 10 mg of nevirapine, to an 8-mL glass stoppered tube. Pipet 2.0 mL of chloroform into the tube. Shake the solution and allow the two phases to separate; then, using a disposable glass Pasteur pipet, remove some of the organic layer from the bottom, and transfer it to another container.

Chromatographic system

(See *Chromatography ⟨621⟩, Thin-Layer Chromatography*.)

Mode: TLC

Adsorbent: 0.25-mm layer of chromatographic silica gel 60 F254

Application volume: 5 µL

Developing solvent system: Ethyl acetate, isopropanol, and concentrated ammonium hydroxide (18:2:0.1)

Spray reagent: 1.35 g of ferric chloride in 25 mL of water and 1.64 g of potassium ferricyanide in 25 mL of water. Mix the two solutions immediately before use.

Analysis

Samples: *Standard solution* and *Sample solution*

Develop in a chamber saturated with a solvent system until the solvent front has moved 6–7 cm from the point of application. Remove the plate from the chamber, mark the solvent front, and dry. Examine under UV light at 254 nm, and outline the spots with a soft pencil. Spray the plate with *Spray reagent*.

Acceptance criteria: The R_F value (approximately 0.4–0.5) of the principal blue spot, under UV and after spraying, from the *Sample solution*, corresponds to that from the *Standard solution*.

• **B.** The retention time of the major peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay*.

ASSAY

• **Procedure**

Diluent: Methanol and water (1:4)

Solution A: 13.6 g of monobasic potassium phosphate in 1900 mL of water. Adjust with phosphoric acid to a pH of 3.0, and dilute with water to 2000 mL.

Solution B: Acetonitrile and *Solution A* (3:97)

Solution C: Acetonitrile and *Solution A* (24:76)

Mobile phase: See the gradient table below.

Time (min)	Solution B (%)	Solution C (%)
0	100	0
1	100	0
31	0	100
32	100	0

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Time (min)	Solution B (%)	Solution C (%)
42	100	0

Standard stock solution: Dissolve 50 mg of USP Nevirapine Anhydrous RS in 20 mL of methanol in a 50-mL volumetric flask. Sonicate with intermittent swirling until the sample dissolves. Add water to 1 cm below the meniscus, cool to room temperature, and dilute with water to volume. The concentration is 1 mg/mL of nevirapine.

Standard solution: 0.3 mg/mL of nevirapine from the *Standard stock solution* diluted with *Diluent*

Stock impurity solution: 3 mg of USP Nevirapine Related Compound A RS and 3 mg of USP Nevirapine Related Compound B RS in 20 mL of methanol in a 100-mL volumetric flask. Sonicate to dissolve. Add water to 1 cm below the meniscus, cool to room temperature, and dilute with water to volume.

System suitability solution: Transfer 15.0 mL of *Standard stock solution* and 2.0 mL of *Stock impurity solution* to a 50-mL volumetric flask, and dilute with *Diluent* to volume.

Weight determination: Using a 1- to 10-mL suitable pipet and a positive displacement tip, withdraw 5.0 mL of Oral Suspension. The sample should be free of air bubbles. Dispense into a tared vial, and record the weight of the Oral Suspension to ±0.1 mg.

Sample solution: Using a 1- to 10-mL suitable pipet and a positive displacement tip, withdraw Oral Suspension equivalent to 60 mg of nevirapine. The sample should be free of air bubbles. Remove the excess Oral Suspension by wiping the outside of the tip carefully so as not to touch the opening of the tip, and deliver the sample into a 200-mL tared volumetric flask. Record the sample weight to the nearest ±0.1 mg. Add 40 mL of methanol, and sonicate for 5 min with intermittent swirling. Add water to 1 cm below the meniscus. Do not shake the flask. Allow the solution to attain room temperature, and dilute with water to volume. Shake the flask gently, and allow to stand for 5 min.

Chromatographic system

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

Mode: LC

Detector: UV 254 nm

Column: 4.6-mm × 15-cm; 3.5-µm packing L10

Guard column: 4.6-mm × 12.5-mm; 5-µm packing L10

Column temperature: 35°

Flow rate: 1.5 mL/min

Injection size: 20 µL

System suitability

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

Suitability requirements

Resolution: NLT 3.0 between nevirapine and nevirapine related compound A; NLT 1.7 between nevirapine and nevirapine related compound B, *System suitability solution*

Tailing factor: NMT 1.5 for the nevirapine peak, *System suitability solution*

Relative standard deviation: NMT 2.0%, *Standard solution*

Analysis

Samples: *Standard solution* and *Sample solution*

Measure the responses for the nevirapine peak. Calculate the percentage of $C_{15}H_{14}N_4O$ in the portion of Oral Suspension 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 Nevirapine Anhydrous RS in the *Standard solution* (mg/mL)

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

Acceptance criteria: 90.0%–110.0%

PERFORMANCE TESTS

• **Dissolution ⟨711⟩**

Medium: 0.1 N hydrochloric acid; 900 mL

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Apparatus 2: 25 rpm

Time: 45 min

Analysis: Determine the amount of $C_{15}H_{14}N_4O$ dissolved by using the following method.

Diluent: Dehydrated alcohol and water (1:1)

Mobile phase: Acetonitrile and water (23:77)

System suitability solution: Transfer 10 mg of USP Nevirapine Anhydrous RS and 15 mg of methylparaben to a 250-mL volumetric flask, dissolve with 2 mL of *Diluent*, and dilute with *Medium* to volume.

Standard solution: Transfer 28 mg of USP Nevirapine Anhydrous RS to a 500-mL volumetric flask, add 2 mL of *Diluent*, and sonicate for 1 min. The Standard will not be completely dissolved at this point. Dilute with *Medium* to volume, and visually examine the solution to ensure that the Standard is completely dissolved. The final concentration is 0.056 mg/mL of nevirapine.

Sample solution: For sample mixing, gently shake the bottle for approximately 10 s by inverting it slowly and rotating it from side to side. The sample should be free of air bubbles. Do not sonicate the sample. Using a 1- to 10-mL suitable positive displacement pipet set at 5 mL, withdraw the equivalent of 50 mg of nevirapine. Remove excess Oral Suspension by wiping the outside of the tip carefully so as not to touch the opening of the tip. Introduce the sample into the dissolution vessel over a period of 1–2 s by immersing the tip of the pipet midway between the paddle and the side of the vessel, approximately 1 cm below the meniscus. Similarly dispense the Oral Suspension into the other vessels. At 45 min, withdraw 5 mL of the solution under test, and pass through a nylon filter of 0.45-µm pore size, discarding the first 2 mL.

Chromatographic system

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

Mode: LC

Detector: UV 214 nm

Column: 3.9-mm × 15-cm; 5-µm packing L1

Guard column: 3.9-mm × 20-mm; packing L1

Flow rate: 1 mL/min

Injection size: 10 µL

System suitability

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

Suitability requirements

Resolution: NLT 5.0 between nevirapine and methylparaben, *System suitability solution*

Tailing factor: NMT 1.8, *System suitability solution*

Relative standard deviation: NMT 2.0%, *Standard solution*

Analysis

Samples: *Standard solution* and *Sample solution*

Record the chromatograms for at least 14 min, and measure the responses for the nevirapine peaks.

Calculate the percentage of $C_{15}H_{14}N_4O$ dissolved:

$$\text{Result} = (r_U \times C_S \times V_1)/(r_S \times V_2 \times L) \times 100$$

r_U = peak response from the *Sample solution*

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

V_1 = volume of the *Medium*, 900 mL

r_S = peak response from the *Standard solution*

V_2 = volume of Oral Suspension taken (mL)

L = label claim (mg/mL)

Tolerances: NLT 80% (Q) of the labeled amount of $C_{15}H_{14}N_4O$ is dissolved.

IMPURITIES

Organic Impurities

- **Procedure**

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

Standard stock solution: Use the *Standard stock solution*, prepared as directed in the *Assay*.

Standard solution: 0.3 µg/mL of nevirapine from the *Standard stock solution* diluted with *Diluent*

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System suitability solution: Prepare as directed in the *Assay*.

Weight determination: Use the weight obtained as directed for *Weight determination* in the *Assay*.

Sample solution: Prepare as directed in the *Assay*.

Chromatographic system

Mode: LC

Detector: UV 254 nm

Column: 4.6-mm × 15-cm; 3.5-µm packing L10

Column temperature: 35°

Flow rate: 1.5 mL/min

Injection size: 20 µL

System suitability

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

Suitability requirements

Resolution: NLT 3.0 between nevirapine and nevirapine related compound A and NLT 1.7 between nevirapine and nevirapine related compound B, *System suitability solution*

Tailing factor: NMT 1.5 for nevirapine, *System suitability solution*

Relative standard deviation: NMT 10.0%, *Standard solution*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of each unknown impurity in the portion of Oral Suspension taken:

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

r_U = peak response for each impurity from the *Sample solution*

r_S = peak response for nevirapine from the *Standard solution*

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

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

Acceptance criteria

Individual unknown impurities: NMT 0.1%

Total unknown impurities: NMT 0.2%

[NOTE—The excipients and their degradation products should not be included in the determination of impurities.]

SPECIFIC TESTS

• **MICROBIAL ENUMERATION TESTS ⟨61⟩** and **TESTS FOR SPECIFIED MICROORGANISMS ⟨62⟩:** It meets the requirements of the tests for absence of *Escherichia coli*. The total aerobic microbial count does not exceed 100 cfu/mL, and the total combined molds and yeasts count does not exceed 50 cfu/mL.

ADDITIONAL REQUIREMENTS

• **PACKAGING AND STORAGE:** Preserve in well-closed containers. Store at 25°, excursions permitted between 15° and 30°.

• **USP REFERENCE STANDARDS ⟨11⟩**

USP Nevirapine Anhydrous RS

USP Nevirapine Related Compound A RS

5,11-Dihydro-6*H*-11-ethyl-4-methyl- dipyrido[3,2-*b*:2',3'-e][1,4]diazepin-6-one.

$C_{14}H_{14}N_4O$ 254.29

USP Nevirapine Related Compound B RS

5,11-Dihydro-4-methyl-6*H*-dipyrido[3,2-*b*:2',3'-e][1,4]diazepin-6-one.

$C_{12}H_{10}N_4O$ 226.23

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

Topic/Question	Contact	Expert Committee
NEVIRAPINE ORAL SUSPENSION	Documentary Standards Support	SM12020 Small Molecules 1

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Topic/Question	Contact	Expert Committee
REFERENCE STANDARD SUPPORT	RS Technical Services RSTECH@usp.org	SM12020 Small Molecules 1

Chromatographic Database Information: Chromatographic Database

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