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Carbidopa and Levodopa Orally Disintegrating Tablets

DEFINITION

To view the Notice from the Expert Committee that posted in conjunction with this accelerated revision, please click *www.uspnf.com/rb-carbidopa-levodopa-odt-20220429*.

Carbidopa and Levodopa Orally Disintegrating Tablets contain NLT 90.0% and NMT 110.0% of the labeled amounts of carbidopa ($C_{10}H_{14}N_2O_4$) and levodopa ($C_9H_{11}NO_4$).

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*.

ASSAY

• **Procedure**

Protect the volumetric solutions from light.

Buffer: 6.6 g/L of monobasic sodium phosphate in water, adjusted with phosphoric acid to a pH of 2.2

Mobile phase: Alcohol and *Buffer* (5:95)

Standard solution: 0.025 mg/mL of USP Carbidopa RS and 0.25 mg/mL of USP Levodopa RS in *Mobile phase*

Sample stock solution: Transfer NLT 10 Tablets to a 1-L volumetric flask. Add 750 mL of *Mobile phase*, sonicate for 20 min, and then stir for 20 min. Dilute with *Mobile phase* to volume.

Sample solution: Dilute the *Sample stock solution* with *Mobile phase* to obtain a nominal concentration of carbidopa of between 0.025 and 0.07 mg/mL and a nominal concentration of levodopa of 0.25 mg/mL.

Chromatographic system

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

Mode: LC

Detector: UV 280 nm

Column: 4.6-mm × 25-cm; 5-µm packing L1

Autosampler temperature: 6°

Flow rate: 1 mL/min

Injection volume: 20 µL

System suitability

Sample: *Standard solution*

[Note—The relative retention times for levodopa and carbidopa are 0.42 and 1.0, respectively.]

Suitability requirements

Tailing factor: NMT 2.4 for both the levodopa and carbidopa peaks

Relative standard deviation: NMT 2.0% for both carbidopa and levodopa

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amounts of carbidopa ($C_{10}H_{14}N_2O_4$) and levodopa ($C_9H_{11}NO_4$) in the portion of Tablets taken:

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

r_U = peak response of carbidopa or levodopa from the *Sample solution*

r_S = peak response of carbidopa or levodopa from the *Standard solution*

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

C_U = nominal concentration of carbidopa or levodopa in the *Sample solution* (mg/mL)

Acceptance criteria: 90.0%–110.0% each of the labeled amounts of carbidopa and levodopa

PERFORMANCE TESTS

• **Disintegration ⟨701⟩:** NMT 60 s

• **Dissolution ⟨711⟩**

Test 1

Medium: 0.1 N hydrochloric acid; 750 mL

Apparatus 2: 50 rpm

Time: 10 min

Solution A: 0.24 g/L of sodium 1-decanesulfonate in water

Mobile phase: Dissolve 11.0 g of monobasic sodium phosphate monohydrate in 1 L of water. Add 1.3 mL of *Solution A*, and adjust with phosphoric acid to a pH of 2.8.

Standard solution: (*L*/800) mg/mL each of USP Carbidopa RS and USP Levodopa RS in *Medium*, where *L* is the label claim in mg/Tablet of carbidopa or levodopa

Sample solution: Pass a portion of the solution under test through a suitable filter of 0.45-µm pore size, and discard the first 3 mL.

Chromatographic system

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

Mode: LC

Detector: UV 280 nm

Column: 4.6-mm × 15.0-cm; 5-µm packing L1

Autosampler temperature: 4°

Flow rate: 2 mL/min

Injection volume: 20 µL

System suitability

Sample: *Standard solution*

[NOTE—The relative retention times for levodopa and carbidopa are 0.4 and 1.0, respectively.]

Suitability requirements

Tailing factor: NMT 2.0 for both levodopa and carbidopa

Relative standard deviation: NMT 2.0% for both levodopa and carbidopa

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amounts of carbidopa ($C_{10}H_{14}N_2O_4$) and levodopa ($C_9H_{11}NO_4$) dissolved:

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

r_U = peak response of carbidopa or levodopa from the *Sample solution*

r_S = peak response of carbidopa or levodopa from the *Standard solution*

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

V = volume of the *Medium*, 750 mL

L = label claim of carbidopa or levodopa (mg/Tablet)

Tolerances: NLT 75% (*Q*) of the labeled amount of carbidopa ($C_{10}H_{14}N_2O_4$) is dissolved, and NLT 75% (*Q*) of the labeled amount of levodopa ($C_9H_{11}NO_4$) is dissolved.

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

Medium: 0.1 N hydrochloric acid; 750 mL, degassed

Apparatus 2: 75 rpm

Time: 15 min

Solution A: 0.24 g/L of sodium 1-decanesulfonate in water

Mobile phase: 12.5 g/L of monobasic sodium phosphate dihydrate prepared as follows. Transfer an appropriate amount of monobasic sodium phosphate dihydrate to a suitable volumetric flask. Dissolve in 95% of the flask volume of water. Add 0.13% of the flask volume of *Solution A*, and adjust with phosphoric acid to a pH of 2.8 ± 0.05. Dilute with water to volume.

Standard stock solution 1: 0.19 mg/mL of USP Carbidopa RS in *Medium*. Transfer an appropriate amount of USP Carbidopa RS to a suitable volumetric flask. Add about 60% of the flask volume of *Medium* and sonicate to promote dissolution. Allow the solution to cool to room temperature and dilute with *Medium* to volume.

Standard stock solution 2: 1.1 mg/mL of USP Levodopa RS in *Medium*. Transfer an appropriate amount of USP Levodopa RS to a suitable volumetric flask. Add about 60% of the flask volume of *Medium* and sonicate to promote dissolution. Allow the solution to cool to room temperature and dilute with *Medium* to volume.

Standard solution

For Tablets labeled to contain 10 mg of carbidopa and 100 mg of levodopa: 0.015 mg/mL of USP Carbidopa RS from *Standard stock solution 1* and 0.13 mg/mL of USP Levodopa RS from *Standard stock solution 2* in *Medium*

For Tablets labeled to contain 25 mg of carbidopa and 100 or 250 mg of levodopa: 0.038 mg/mL of USP Carbidopa RS from *Standard stock solution 1* and 0.22 mg/mL of USP Levodopa RS from *Standard stock solution 2* in *Medium*

Sample solution: Pass a portion of the solution under test through a suitable filter of 0.45-µm pore size, and discard the first 2 mL.

Chromatographic system

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

Mode: LC

Detector: UV 280 nm

Column: 3.9-mm × 30.0-cm; 10-µm packing L1

Flow rate: 2 mL/min

Injection volume: 20 µL

Run time: NLT 1.3 times the retention time of carbidopa

System suitability

Sample: *Standard solution*

[NOTE—The relative retention times for levodopa and carbidopa are 0.4 and 1.0, respectively.]

Suitability requirements

Resolution: NLT 6 between levodopa and carbidopa

Tailing factor: NMT 2.0 for both levodopa and carbidopa

Relative standard deviation: NMT 2.0% for both levodopa and carbidopa

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amounts of carbidopa ($C_{10}H_{14}N_2O_4$) and levodopa ($C_9H_{11}NO_4$) dissolved:

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

r_U = peak response of carbidopa or levodopa from the *Sample solution*

r_S = peak response of carbidopa or levodopa from the *Standard solution*

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

V = volume of the *Medium*, 750 mL

L = label claim of carbidopa or levodopa (mg/Tablet)

Tolerances: NLT 75% (*Q*) of the labeled amount of carbidopa ($C_{10}H_{14}N_2O_4$) is dissolved, and NLT 75% (*Q*) of the labeled amount of levodopa ($C_9H_{11}NO_4$) is dissolved.

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

IMPURITIES

Change to read:

• **ORGANIC IMPURITIES**

Protect all analytical solutions from light, and maintain them at 2°–8° until they are injected.

Diluent: Methanol and 0.1 N hydrochloric acid (30:70)

Mobile phase: 13.8 g/L of monobasic sodium phosphate monohydrate in water, adjusted with phosphoric acid to a pH of 2.7

System suitability solution: 0.025 mg/mL each of USP Carbidopa RS, USP Levodopa RS, USP Levodopa Related Compound A RS, USP Levodopa Related Compound B RS, and USP Methyldopa RS in *Diluent*

Standard solution: 0.025 mg/mL of USP Levodopa RS in *Diluent*

Sample solution: Transfer a weighed quantity of powder equivalent to 250 mg of levodopa from NLT 20 finely powdered Tablets to a 100-mL volumetric flask. Add 80 mL of *Diluent*, sonicate for 10 min, and then stir for 30 min. Dilute with *Diluent* to volume. Centrifuge, and inject the supernatant within 2 h.

Chromatographic system

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

Mode: LC

Detector: UV 280 nm

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

Autosampler temperature: 4°

Flow rate: 1.5 mL/min

Injection volume: 20 µL

Run time: 6 times the retention time of carbidopa

System suitability

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

[NOTE—For the relative retention times, see *Table 1*. If peak fronting for levodopa related compound A is observed, lowering the column temperature to 15° is recommended to eliminate this problem.]

Suitability requirements

Resolution: NLT 1.5 between levodopa related compound A and levodopa, NLT 2.0 between carbidopa and levodopa related compound B, and NLT 1.5 between methyldopa and carbidopa; *System suitability solution*

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

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of all impurities and any unspecified degradation product other than methyldopa and 3,4-dihydroxyphenylacetone, based on the label claim of levodopa 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 levodopa related compound A or any unspecified degradation product from the *Sample solution*

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

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

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

F = relative response factor (see *Table 1*)

Calculate the percentage of methyldopa and 3,4-dihydroxyphenylacetone based on the label claim of carbidopa 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 methyldopa or 3,4-dihydroxyphenylacetone from the *Sample solution*

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

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

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

F = relative response factor (see *Table 1*)

Acceptance criteria: See *Table 1*.

Table 1

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Levodopa related compound A[a]	0.45	0.80	0.2
Levodopa	0.52	—	—
Methyldopa[b]	0.84	1.0	▲0.6▲ (RB 1-May-2022)
Carbidopa	1.0	—	—
Levodopa related compound B[c]	1.2	—	—
3-*O*-Methyl carbidopa[c,d]	3.1	—	—
3,4-Dihydroxyphenylacetone[b,d]	3.9	1.0	1.0
Any individual unspecified degradation product[a]	—	1.0	0.2
Total impurities[e]	—	—	1.0

[a] Individual impurity based on the label claim of levodopa.

[b] Individual impurity based on the label claim of carbidopa.

[c] Process-related impurities, included for identification only; not to be included in total impurities.

[d] (*S*)-2-Hydrazinyl-3-(4-hydroxy-3-methoxyphenyl)-2-methylpropanoic acid.

[e] Excluding all process impurities and 3,4-dihydroxyphenylacetone.

ADDITIONAL REQUIREMENTS

• **Packaging and Storage:** Preserve in well-closed, light-resistant containers, and store at controlled room temperature.

• **Labeling:** The labeling states the *Dissolution* test used only if *Test 1* is not used.

Change to read:

• **USP Reference Standards** ⟨11⟩

USP Carbidopa RS

USP Levodopa RS

USP Levodopa Related Compound A RS

▲3-(2,4,5-Trihydroxyphenyl)-*L*-alanine▲ (RB 1-May-2022)

$C_9H_{11}NO_5$ 213.19

USP Levodopa Related Compound B RS

3-Methoxytyrosine.

$C_{10}H_{13}NO_4$ ▲211.22▲ (RB 1-May-2022)

USP Methyldopa RS

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

Topic/Question	Contact	Expert Committee
CARBIDOPA AND LEVODOPA ORALLY DISINTEGRATING TABLETS	Documentary Standards Support	SM42020 Small Molecules 4

Chromatographic Database Information: Chromatographic Database

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