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Carbidopa and Levodopa Tablets

To view the Notice from the Expert Committee that posted in conjunction with this accelerated revision, please click https://www.uspnf.com/rb-carbidopa-levodopa-tabs-20230929.

DEFINITION

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

IDENTIFICATION

• **A.** The UV spectra of the carbidopa and levodopa peaks of *Sample solution A* and *Sample solution B*, respectively, correspond to those of the *Standard solution*, as obtained in the *Assay*.

• **B.** The retention times of the carbidopa and levodopa peaks of *Sample solution A* and *Sample solution B*, respectively, correspond to those of the *Standard solution*, as obtained in the *Assay*.

ASSAY

• **Procedure**

Protect solutions containing carbidopa or levodopa from light and maintain them at 2°–8° until they are injected. Use within 12 h.

Buffer: 6 g/L of anhydrous monobasic sodium phosphate in water, adjusted with phosphoric acid to a pH of 2.2

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

Standard solution: 125 µg/mL of USP Carbidopa RS and 125 µg/mL of USP Levodopa RS in *Mobile phase*

System suitability solution: 2.5 µg/mL of USP Levodopa Related Compound B RS in *Standard solution*

Sample solution A: Nominally 125 µg/mL of carbidopa from Tablets prepared as follows. Transfer a suitable portion of powder from Tablets (NLT 10) to an appropriate volumetric flask. Add 80% of the total flask volume of *Mobile phase*. Sonicate for 15 min with intermittent shaking. Dilute with *Mobile phase*. Centrifuge the resulting solution and use the supernatant.
[Note—The use of a centrifuge speed of 3000 rpm for 5 min may be suitable.]

Sample solution B: Nominally 125 µg/mL of levodopa from *Sample solution A* in *Mobile phase*

Chromatographic system

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

Mode: LC

Detector: UV 280 nm. For *Identification A,* use a diode array detector in the range of 210–400 nm.

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

Autosampler temperature: 5°

Flow rate: 1 mL/min

Injection volume: 20 µL

Run time: NLT 5 times the retention time of carbidopa

System suitability

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

[Note—See *Table 1* for the relative retention times.]

Suitability requirements

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

Tailing factor: NMT 2.0 each for levodopa and carbidopa, *Standard solution*

Relative standard deviation: NMT 1.0% each for levodopa and carbidopa, *Standard solution*

Analysis

Samples: *Standard solution*, *Sample solution A*, and *Sample solution B*

Calculate the percentage of the labeled amount of carbidopa ($C_{10}H_{14}N_2O_4$) 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 from *Sample solution A*

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

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

C_U = nominal concentration of carbidopa in *Sample solution A* (µg/mL)

Calculate the percentage of the labeled amount of 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 levodopa from *Sample solution B*

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

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

C_U = nominal concentration of levodopa in *Sample solution B* (µg/mL)

Acceptance criteria: 90.0%–110.0% of the labeled amount of carbidopa; 90.0%–110.0% of the labeled amount of levodopa

PERFORMANCE TESTS

Change to read:

• **Dissolution** ⟨711⟩

Test 1

Medium: 0.1 N hydrochloric acid; 750 mL

Apparatus 1: 50 rpm

Time: 30 min

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

Mobile phase: 11.0 g/L of monobasic sodium phosphate in solution, prepared as follows. Transfer a sufficient quantity of monobasic sodium phosphate into a container, and dissolve in water, using 95% of the total volume. Add 0.13% of the total volume of *Diluent*, and adjust with phosphoric acid to a pH of 2.8. Transfer to a suitable volumetric flask, and dilute with water to volume.

Standard solution: (L_1/750) mg/mL of USP Levodopa RS and (L_2/750) mg/mL of USP Carbidopa RS in *Medium*, where L_1 and L_2 are the label claims of levodopa and carbidopa, respectively, in mg/Tablet

Sample solution: A filtered portion of the solution under test

Chromatographic system

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

Mode: LC

Detector: UV 280 nm

Column: 3.9-mm × 30-cm; 10-µm packing L1

Flow rate: 2 mL/min

Injection volume: 20 µL

Run time: NLT 2 times the retention time for 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

Relative standard deviation: NMT 2.0% for levodopa; NMT 2.0% for carbidopa

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount 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 80% (Q) of the labeled amount of carbidopa ($C_{10}H_{14}N_2O_4$) and levodopa ($C_9H_{11}NO_4$) are 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

Apparatus 1: 100 rpm

Time: 15 min

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

Mobile phase: 11.0 g/L of monobasic sodium phosphate in solution, prepared as follows. Transfer a sufficient quantity of monobasic sodium phosphate into a container, and dissolve in water, using 95% of the final volume. Add 0.13% of the final volume of *Solution A*, and adjust with phosphoric acid to a pH of 2.8. Transfer to a suitable volumetric flask, and dilute with water to volume.

Standard solution: (L_1/750) mg/mL of USP Levodopa RS and (L_2/750) mg/mL of USP Carbidopa RS in *Medium*, where L_1 and L_2 are the label claims of levodopa and carbidopa, respectively, in mg/Tablet

Sample solution: Pass a portion of the solution under test through a suitable filter.

Chromatographic system

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

Mode: LC

Detector: UV 280 nm

Column: 3.9-mm × 30-cm; 10-µm packing L1

Flow rate: 2 mL/min

Injection volume: 40 µL

Run time: NLT 2 times the retention time for 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

Relative standard deviation: NMT 2.0% for levodopa; NMT 2.0% for carbidopa

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount 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 80% (Q) of the labeled amount of carbidopa ($C_{10}H_{14}N_2O_4$) and levodopa ($C_9H_{11}NO_4$) are dissolved.

Test 3: If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 3*.

Medium: 0.1 N hydrochloric acid; 750 mL, deaerated

Apparatus 1: 65 rpm

Time: 30 min

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

Mobile phase: 12.5 g/L of monobasic sodium phosphate dihydrate in solution, prepared as follows. Transfer a sufficient quantity of monobasic sodium phosphate dihydrate into a suitable volumetric flask, and dissolve in water, using 95% of the final volume. Add 0.13% of the final volume of *Solution A*, and adjust with phosphoric acid to a pH of 2.8. Dilute with water to volume.

Carbidopa standard stock solution: 0.19 mg/mL of USP Carbidopa RS in *Medium*. Sonicate to dissolve if necessary.

Levodopa standard stock solution: 1.1 mg/mL of USP Levodopa RS in *Medium*. Sonicate to dissolve if necessary.

Standard solution

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

For Tablets labeled to contain 10-mg carbidopa/100-mg levodopa: 0.015 mg/mL of USP Carbidopa RS from *Carbidopa standard stock solution* and 0.132 mg/mL of USP Levodopa RS from *Levodopa standard stock solution* in *Medium*

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

Chromatographic system

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

Mode: LC

Detector: UV 280 nm

Column: 3.9-mm × 30-cm; 10-µm packing L1

Flow rate: 2 mL/min

Injection volume: 20 µL

Run time: NLT 2 times the retention time for 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

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

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount 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 80% (Q) of the labeled amount of carbidopa ($C_{10}H_{14}N_2O_4$) and levodopa ($C_9H_{11}NO_4$) are dissolved.

▲**Test 4:** If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 4*.

Medium: 0.1 N hydrochloric acid; 500 mL

Apparatus 1: 100 rpm

Time: 30 min

Mobile phase: Dissolve 13.6 g of potassium phosphate, monobasic in 1000 mL of water. Adjust with phosphoric acid to a pH of 3.0.

Standard solution: (L_1/500) mg/mL of USP Levodopa RS and (L_2/500) mg/mL of USP Carbidopa RS in *Medium*, where L_1 and L_2 are the label claims of levodopa and carbidopa, respectively, in mg/Tablet. Sonicate to dissolve.

Sample solution: Pass a portion of the solution under test through a suitable filter of 0.45-µm pore size, discarding an appropriate volume of filtrate so that a consistent result can be obtained.

Chromatographic system

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

Mode: LC

Detector: UV 282 nm

Column: 4.6-mm × 15-cm; 3.5-µm packing L7

Flow rate: 1.5 mL/min

Injection volume: 20 µL

Run time: NLT 1.8 times the retention time for carbidopa

System suitability

Sample: *Standard solution*

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

Suitability requirements

Tailing: NMT 2.0 for levodopa; NMT 2.0 for carbidopa

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

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount 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*, 500 mL

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

Tolerances: NLT 80% (Q) of the labeled amount of carbidopa ($C_{10}H_{14}N_2O_4$) and levodopa ($C_9H_{11}NO_4$) are dissolved.▲ (RB 1-Oct-2023)

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

IMPURITIES

• Organic Impurities

Protect solutions containing carbidopa or levodopa from light and maintain them at 2°–8° until they are injected. Use within 12 h.

Mobile phase and **Chromatographic system:** Proceed as directed in the *Assay*.

System suitability solution: 125 µg/mL of USP Carbidopa RS, 0.25 µg/mL of dihydroxybenzaldehyde, 1.25 µg/mL of dihydroxyphenylacetone, and 2.5 µg/mL of USP Levodopa Related Compound B RS in *Mobile phase*

Standard solution: 1.25 µg/mL of USP Carbidopa RS and 5 µg/mL of USP Levodopa RS in *Mobile phase*

Sample solution: Nominally 125 µg/mL of carbidopa from Tablets prepared as follows. Transfer a suitable amount of powder from Tablets (NLT 10) to an appropriate volumetric flask. Add 80% of the total flask volume of *Mobile phase*. Sonicate for 15 min with intermittent shaking. Dilute with *Mobile phase*. Centrifuge the resulting solution and use the supernatant.

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

System suitability

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

[Note—See *Table 1* for the relative retention times.]

Suitability requirements

Resolution: NLT 1.5 between levodopa related compound B and carbidopa; NLT 1.5 between dihydroxybenzaldehyde and dihydroxyphenylacetone, *System suitability solution*

Relative standard deviation: NMT 3.0% each for levodopa and carbidopa, *Standard solution*

Signal-to-noise ratio: NLT 10 for dihydroxybenzaldehyde and dihydroxyphenylacetone, *System suitability solution*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of methyldopa and dihydroxyphenylacetone 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 dihydroxyphenylacetone from the *Sample solution*

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

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

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

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

Calculate the percentage of any unspecified 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 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* (µg/mL)

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

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

Acceptance criteria: See *Table 1*. The reporting thresholds are 0.1% and 0.05% for peaks associated with carbidopa and levodopa, respectively.

Table 1

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Levodopa related compound A[a,b]	0.8	—	—
Levodopa	1.0	—	—
Methyldopa	1.8	1.0	0.7

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Levodopa related compound B[a]	2.0	—	—
Carbidopa	2.3	—	—
Dihydroxybenzaldehyde[a,c]	5.6	—	—
Dihydroxyphenylacetone[d]	6.2	1.4	1
Carbidopa related compound A[a,e]	6.6	—	—
Any unspecified degradation product	—	1.0	0.2
Total degradation products	—	—	4.0

[a] Process impurity is 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 for the drug product.

[b] 3-(2,4,5-Trihydroxyphenyl)-L-alanine.

[c] 3,4-Dihydroxybenzaldehyde.

[d] 3,4-Dihydroxyphenylacetone.

[e] (*S*)-2-Hydrazinyl-3-(4-hydroxy-3-methoxyphenyl)-2-methylpropanoic acid; also known as 3-*O*-methylcarbidopa.

ADDITIONAL REQUIREMENTS

- **Packaging and Storage:** Dispense in a tight, light-resistant container. Store at controlled room temperature.
- **Labeling:** The labeling states the *Dissolution* test used only if *Test 1* is not used.
- **USP Reference Standards** ⟨11⟩

USP Carbidopa RS

USP Levodopa RS

USP Levodopa Related Compound B RS

3-Methoxy-L-tyrosine;
Also known as 3-Methoxytyrosine.
$C_{10}H_{13}NO_4$ 211.22

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

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

Chromatographic Database Information: Chromatographic Database

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