Carbidopa and Levodopa Orally Disintegrating Tablets

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Expert Committee	Chemical Medicines Monographs 4
Reason for Revision	Compliance

In accordance with the Rules and Procedures of the 2015–2020 Council of Experts, the Chemical Medicines Monographs 4 Expert Committee has revised the Carbidopa and Levodopa Orally Disintegrating Tablets monograph. The purpose for the revision is to add *Dissolution Test 2* to accommodate FDA-approved drug products with different dissolution conditions than the existing dissolution test. Additionally, a *Labeling* section has been added.

- *Dissolution Test 2* was validated using a µBondapak C18 brand of L1 column. The typical retention times for levodopa and carbidopa are about 4 and 11 min, respectively.

The Carbidopa and Levodopa Orally Disintegrating Tablets Revision Bulletin supersedes the currently official monograph.

Should you have any questions, please contact Heather Joyce, Ph.D., Senior Scientific Liaison (301-998-6792 or hrj@usp.org).

Carbidopa and Levodopa Orally Disintegrating Tablets

DEFINITION

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

Change to read:

• **DISSOLUTION ⟨711⟩**

▲**Test 1**▲ (RB 1-Jun-2018)

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.▲ (RB 1-Jun-2018)

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

IMPURITIES

• **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*
C_U = nominal concentration of carbidopa in the *Sample solution*
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	0.5
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.

Add the following:

▲• **LABELING:** The labeling states the *Dissolution* test used only if *Test 1* is not used.▲ (RB 1-Jun-2018)

- **USP REFERENCE STANDARDS ⟨11⟩**
  USP Carbidopa RS
  USP Levodopa RS
  USP Levodopa Related Compound A RS
  3-(3,4,6-Trihydroxyphenyl)alanine.
  $C_9H_{11}NO_5$ 213.19
  USP Levodopa Related Compound B RS
  3-Methoxytyrosine.
  $C_{10}H_{13}NO_4$ 211.21
  USP Methyldopa RS