Carbidopa and Levodopa Extended-Release Tablets

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Expert Committee	Chemical Medicines Monographs 4

In accordance with section 7.04 (c) of the 2015–2020 Rules and Procedures of the Council of Experts and the Pending Monograph Guideline, this is to provide notice that the Chemical Medicines Monographs 4 Expert Committee intends to revise the Carbidopa and Levodopa Extended-Release Tablets monograph.

Comments with supporting data were received that indicate that the existing dissolution tests are not suitable for all relevant drug products. The Expert Committee proposes to revise the Carbidopa and Levodopa Extended-Release Tablets monograph to add *Dissolution Test 7* to accommodate drug products that are anticipated to be approved with different dissolution conditions and tolerances. Additionally, the chemical name for levodopa related compound A and the table number within the test for *Organic Impurities* were updated.

- *Dissolution Test 7* was validated using a Hypersil BDS C18 brand of column with L1 packing. The typical retention times for levodopa and carbidopa are about 2.6 and 5.3 min, respectively.

The proposed revision is contingent on FDA approval of a product that meets the proposed monograph specifications. The proposed revision will be published as a Revision Bulletin and an official date will be assigned to coincide as closely as possible with the FDA approval of the associated product.

See below for additional information about the proposed text.[1]

Should you have any questions, please contact Heather Joyce, Ph.D., Senior Scientific Liaison to the Chemical Medicines Monographs 4 Expert Committee (301-998-6792 or hrj@usp.org).

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[1] This text is not the official version of a *USP–NF* monograph and may not reflect the full and accurate contents of the currently official monograph. Please refer to the current edition of the *USP–NF* for official text.

USP provides this text to indicate changes that we anticipate will be made official once the product subject to this proposed revision under the Pending Monograph Program receives FDA approval. Once FDA approval is granted for the associated revision request, a Revision Bulletin will be posted that will include the changes indicated herein, as well as any changes indicated in the product's final approval, combined with the text of the monograph as effective on the date of approval. Any revisions made to a monograph under the Pending Monograph Program that are posted without prior publication for comment in the *Pharmacopeial Forum* must also meet the requirements outlined in the USP Guideline on Use of Accelerated Processes for Revisions to the *USP–NF*.

Carbidopa and Levodopa Extended-Release Tablets

DEFINITION

Carbidopa and Levodopa Extended-Release 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 retention times of the major peaks of the *Sample solution* correspond to those of the *Standard solution*, as obtained in the *Assay*.

Add the following:

▲• **B.** The UV spectra of the major peaks of the *Sample solution* correspond to those of the *Standard solution*, as obtained in the *Assay*.▲ 1S (USP41)

ASSAY

Change to read:

• **PROCEDURE**

Protect the volumetric preparations from light.

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

Solution B: 11.6 g/L of monobasic sodium phosphate in water

Mobile phase: *Solution A*, *Solution B*, and water (0.13: 95: 4.87), prepared as follows. Add 0.13% of the final volume of *Solution A* to 95% of the final volume of *Solution B*. Adjust with phosphoric acid to a pH of 2.8. Dilute with water to final volume.

Standard solution: 0.1 mg/mL of USP Carbidopa RS and 0.4 mg/mL of USP Levodopa RS in solution, prepared as follows. Transfer accurately weighed portions of the Reference Standards into a suitable volumetric flask, and dissolve in 0.1 N phosphoric acid using 8% of the final volume. Sonication may be used to promote dissolution. Dilute with water to final volume.

Sample solution: Nominally 0.1 mg/mL of carbidopa and 0.4 mg/mL of levodopa from NLT 20 finely powdered Tablets, prepared as follows. Transfer an accurately weighed portion of the powder, equivalent to 1 Tablet weight, into a suitable volumetric flask, and dissolve in 0.1 N phosphoric acid, using 10% of the final volume. Sonicate for 10 min and then stir for 30 min. Dilute with water to volume and stir for another 20 min. Pass the solution through a suitable filter of 0.45-µm pore size.

Chromatographic system

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

Mode: LC

Detector: UV 280 nm. ▲For *Identification B*, use a diode array detector in the range of 200–350 nm.▲ 1S (USP41)

Column: 4.6-mm × 10-cm; 5-µm packing L1

Flow rate: 2 mL/min

Injection volume: 20 µL

▲**Run time:** NLT 4 times the retention time of levodopa▲ 1S (USP41)

System suitability

Sample: *Standard solution*

[NOTE—The relative retention times for levodopa and carbidopa are 1.0 and 2.8, respectively.]

Suitability requirements

Tailing factor: NMT 1.5 for carbidopa; NMT 1.5 for levodopa

Resolution: NLT 6 between levodopa and carbidopa

Relative standard deviation: NMT 1.0% for carbidopa; NMT 1.0% for levodopa

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of carbidopa ($C_{10}H_{14}N_2O_4$) or 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

Change to read:

• **DISSOLUTION** ⟨711⟩

Test 1

Medium: 0.1 N hydrochloric acid; 900 mL degassed with helium

Apparatus 2: 50 rpm

Times

For Tablets that contain 25 mg of carbidopa and 100 mg of levodopa: 0.5, 1, and 4 h

For Tablets that contain 50 mg of carbidopa and 200 mg of levodopa: 0.5, 1, 2.5, and 4 h

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

Solution B: 12.7 g/L of monobasic sodium phosphate in water

Mobile phase: *Solution A*, *Solution B*, and water (0.13: 95: 4.87), prepared as follows. Add 0.13% of the final volume of *Solution A* to 95% of the final volume of *Solution B*. Adjust with phosphoric acid to a pH of 2.8. Dilute with water to final volume.

Standard solution: 0.03 mg/mL of USP Carbidopa RS and 0.1 mg/mL of USP Levodopa RS in *Medium*. Sonication may be used to aid in dissolution.

Sample solution

For Tablets that contain 25 mg of carbidopa and 100 mg of levodopa: Pass a portion of the solution under test through a suitable filter of 0.45-µm pore size and discard the first 1–3 mL.

For Tablets that contain 50 mg of carbidopa and 200 mg of levodopa: Pass a portion of the solution under test through a suitable filter of 0.45-µm pore size, discard the first 1–3 mL, and dilute with *Medium* (50:50).

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 3 times the retention time of levodopa▲ 1S (USP41)

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 2.0 between levodopa and carbidopa
Relative standard deviation: NMT 2.0% for carbidopa and NMT 2.0% for levodopa for six replicate injections

Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the concentration (C_i) of carbidopa ($C_{10}H_{14}N_2O_4$) or levodopa ($C_9H_{11}NO_4$) in the sample withdrawn from the vessel at each time point (*i*):

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

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)
D = dilution factor for the *Sample solution*, if needed

Calculate the percentage of the labeled amount of carbidopa ($C_{10}H_{14}N_2O_4$) or levodopa ($C_9H_{11}NO_4$) dissolved at each time point (*i*):

$$\text{Result}_1 = C_1 \times V \times (1/L) \times 100$$
$$\text{Result}_2 = \{[C_2 \times (V - V_S)] + (C_1 \times V_S)\} \times (1/L) \times 100$$
$$\text{Result}_3 = (\{C_3 \times [V - (2 \times V_S)]\} + [(C_2 + C_1) \times V_S]) \times (1/L) \times 100$$
$$\text{Result}_4 = (\{C_4 \times [V - (3 \times V_S)]\} + [(C_3 + C_2 + C_1) \times V_S]) \times (1/L) \times 100$$

C_i = concentration of carbidopa or levodopa in the portion of sample withdrawn at time point *i* (mg/mL)
V = volume of the *Medium*, 900 mL
L = label claim of carbidopa or levodopa (mg/Tablet)
V_S = volume of the *Sample solution* withdrawn from the *Medium* (mL)

Tolerances
For Tablets that contain 25 mg of carbidopa and 100 mg of levodopa: See *Table 1*.

Table 1

Time Point (*i*)	Time (h)	Amount of Carbidopa Dissolved (%)	Amount of Levodopa Dissolved (%)
1	0.5	15–40	14–39
2	1	37–62	36–61
3	4	NLT 80	NLT 80

For Tablets that contain 50 mg of carbidopa and 200 mg of levodopa: See *Table 2*.

Table 2

Time Point (*i*)	Time (h)	Amount of Carbidopa Dissolved (%)	Amount of Levodopa Dissolved (%)
1	0.5	8–33	8–33
2	1	26–51	26–51
3	2.5	62–87	64–89
4	4	NLT 80	NLT 80

The percentages of the labeled amounts of carbidopa ($C_{10}H_{14}N_2O_4$) and levodopa ($C_9H_{11}NO_4$) dissolved at the times specified conform to *Dissolution* ⟨711⟩, *Acceptance Table 2*.

Test 2: If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 2*.
Medium: Simulated gastric fluid TS (prepared without enzymes); 900 mL
Apparatus 2: 50 rpm
Times: 0.5, 1, 2, and 3 h
Buffer: 6.8 g/L of monobasic potassium phosphate and 1.0 g/L of 1-hexanesulfonic acid in water. Adjust with phosphoric acid to a pH of 3.3.
Mobile phase: Filtered and degassed mixture of methanol and *Buffer* (20:80)
Standard solution: (*L*/900) mg/mL each of USP Carbidopa RS and USP Levodopa RS in *Medium*, where *L* is the label claim, in mg/Tablet
Sample solution: Pass a portion of the solution under test through a suitable filter of 0.45-µm pore size.
Chromatographic system
(See *Chromatography* ⟨621⟩, *System Suitability*.)
Mode: LC
Detector: UV 280 nm
Column: 4.6-mm × 15-cm; 5-µm packing L7
Flow rate: 1 mL/min
Injection volume: 20 µL
▲**Run time:** NLT 2.5 times the retention time of levodopa▲ 1S (USP41)
System suitability
Sample: *Standard solution*
[NOTE—The relative retention times for levodopa and carbidopa are 1.0 and 1.4, respectively.]
Suitability requirements
Resolution: NLT 2.0 between levodopa and carbidopa
Column efficiency: NLT 4000 theoretical plates for both carbidopa and levodopa
Tailing factor: NMT 2.0 for both carbidopa and levodopa
Relative standard deviation: NMT 1.0% for both carbidopa and levodopa
Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the concentration (C_i) of carbidopa ($C_{10}H_{14}N_2O_4$) or levodopa ($C_9H_{11}NO_4$) in the sample withdrawn from the vessel at each time point (*i*):

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

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)

Calculate the percentage of the labeled amount of carbidopa ($C_{10}H_{14}N_2O_4$) or levodopa ($C_9H_{11}NO_4$) dissolved at each time point (*i*):

$$\text{Result}_1 = C_1 \times V \times (1/L) \times 100$$
$$\text{Result}_2 = \{[C_2 \times (V - V_S)] + (C_1 \times V_S)\} \times (1/L) \times 100$$
$$\text{Result}_3 = (\{C_3 \times [V - (2 \times V_S)]\} + [(C_2 + C_1) \times V_S]) \times (1/L) \times 100$$
$$\text{Result}_4 = (\{C_4 \times [V - (3 \times V_S)]\} + [(C_3 + C_2 + C_1) \times V_S]) \times (1/L) \times 100$$

C_i = concentration of carbidopa or levodopa in the portion of sample withdrawn at time point *i* (mg/mL)
V = volume of the *Medium*, 900 mL
L = label claim of carbidopa or levodopa (mg/Tablet)
V_S = volume of the *Sample solution* withdrawn from the *Medium* (mL)

Tolerances: See *Table 3*.

Table 3

Time Point (*i*)	Time (h)	Amount Dissolved (%)
1	0.5	20–35
2	1	35–60
3	2	65–95
4	3	NLT 80

The percentages of the labeled amounts of carbidopa ($C_{10}H_{14}N_2O_4$) and levodopa ($C_9H_{11}NO_4$) dissolved at the times specified conform to *Dissolution* ⟨711⟩, *Acceptance Table 2*.

Test 3: If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 3*.
Medium, Apparatus 2, Solution A, Solution B, Mobile phase, Standard solution, Chromatographic system, and **System suitability:** Proceed as directed in *Test 1*.
Times: 0.5, 1, 2.5, and 4 h
Sample solution: Pass a portion of the solution under test through a suitable filter.
Analysis: Proceed as directed in *Test 1*.
Tolerances: See *Table 4*.

Table 4

Time Point (*i*)	Time (h)	Amount Dissolved for Tablets That Contain 25 mg of Carbidopa and 100 mg of Levodopa (%)	Amount Dissolved for Tablets That Contain 50 mg of Carbidopa and 200 mg of Levodopa (%)
1	0.5	15–40	15–35
2	1	25–65	25–65
3	2.5	NLT 60	NLT 60
4	4	NLT 80	NLT 80

The percentages of the labeled amounts of carbidopa ($C_{10}H_{14}N_2O_4$) and levodopa ($C_9H_{11}NO_4$) dissolved at the times specified conform to *Dissolution* ⟨711⟩, *Acceptance Table 2*.

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; 900 mL
Apparatus 2: 50 rpm
Times: 1, 3, and 6 h
Solution A: 0.24 g/L of sodium 1-decanesulfonate in water
Solution B: 11.6 g/L of monobasic sodium phosphate in water
Mobile phase: *Solution A*, *Solution B*, and water (0.13: 95: 4.87), prepared as follows. Add 0.13% of the final volume of *Solution A* to 95% of the final volume of *Solution B*. Adjust with phosphoric acid to a pH of 2.8. Dilute with water to final volume.
Standard solution: (*L*/900) mg/mL each of USP Carbidopa RS and USP Levodopa RS in *Medium*, where *L* is the label claim, in mg/Tablet
Sample solution: Withdraw a 10.0-mL aliquot at each time point and pass a portion of the solution under test through a suitable filter. Replace the 10.0-mL aliquot withdrawn for analysis with a 10.0-mL aliquot of *Medium*.
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: 50 µL
Run time: NLT 3 times the retention time of levodopa
System suitability
Sample: *Standard solution*
[NOTE—The relative retention times for levodopa and carbidopa are 1.0 and 2.5, respectively.]
Suitability requirements
Resolution: NLT 2.0 between levodopa and carbidopa
Tailing factor: NMT 2.0 for both carbidopa and levodopa
Relative standard deviation: NMT 2.0% for both carbidopa and levodopa
Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the concentration (C_i) of carbidopa ($C_{10}H_{14}N_2O_4$) or levodopa ($C_9H_{11}NO_4$) in the sample withdrawn from the vessel at each time point (*i*):

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

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)

Calculate the percentage of the labeled amount of carbidopa ($C_{10}H_{14}N_2O_4$) or levodopa ($C_9H_{11}NO_4$) dissolved at each time point (*i*):

$$\text{Result}_1 = C_1 \times V \times (1/L) \times 100$$
$$\text{Result}_2 = [(C_2 \times V) + (C_1 \times V_S)] \times (1/L) \times 100$$
$$\text{Result}_3 = [(C_3 \times V) + (C_2 + C_1) \times V_S] \times (1/L) \times 100$$

C_i = concentration of carbidopa or levodopa in the portion of sample withdrawn at time point *i* (mg/mL)
V = volume of the *Medium*, 900 mL
L = label claim of carbidopa or levodopa (mg/Tablet)
V_S = volume of the *Sample solution* withdrawn from the vessel and replaced with *Medium*, 10 mL

Tolerances: See *Table 5*.

Table 5

Time Point (*i*)	Time (h)	Amount Dissolved for Tablets That Contain 25 mg of Carbidopa and 100 mg of Levodopa (%)	Amount Dissolved for Tablets That Contain 50 mg of Carbidopa and 200 mg of Levodopa (%)
1	1	35–70	25–60
2	3	NLT 65	NLT 65
3	6	NLT 80	NLT 80

The percentages of the labeled amounts of carbidopa ($C_{10}H_{14}N_2O_4$) and levodopa ($C_9H_{11}NO_4$) dissolved at the times specified conform to *Dissolution* ⟨711⟩, *Acceptance Table 2*.

Test 5: If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 5*.

Medium: 0.1 N hydrochloric acid; 900 mL

Apparatus 2: 50 rpm

Times: 0.5, 1, 2.5, and 4 h

Mobile phase: 13.6 g/L of monobasic potassium phosphate adjusted with phosphoric acid to a pH of 3.0

Standard solution: (L/900) mg/mL each of USP Carbidopa RS and USP Levodopa RS in *Medium*, where L is the label claim, in mg/Tablet. [NOTE—This solution is stable for 1 day if stored at 23°–27°.]

Sample solution: Pass a portion of the solution under test through a suitable filter of 0.45-µm pore size, and discard the first 4–5 mL. [NOTE—This solution is stable for 1 day if stored at 23°–27°.]

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

Mode: LC

Detector: UV 282 nm

Column: 4.6-mm × 15-cm; 5-µm packing L7

Flow rate: 1.5 mL/min

Injection volume: 20 µL

Run time: NLT 3 times the retention time of levodopa

System suitability

Sample: *Standard solution*
[NOTE—The relative retention times for levodopa and carbidopa are 1.0 and 1.6, respectively.]

Suitability requirements

Resolution: NLT 2.0 between levodopa and carbidopa

Tailing factor: NMT 2.0 for both carbidopa and levodopa

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

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the concentration (C_i) of carbidopa ($C_{10}H_{14}N_2O_4$) or levodopa ($C_9H_{11}NO_4$) in the sample withdrawn from the vessel at each time point (*i*):

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

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)

Calculate the percentage of the labeled amount of carbidopa ($C_{10}H_{14}N_2O_4$) or levodopa ($C_9H_{11}NO_4$) dissolved at each time point (*i*):

$$\text{Result}_1 = C_1 \times V \times (1/L) \times 100$$
$$\text{Result}_2 = \{[C_2 \times (V - V_S)] + (C_1 \times V_S)\} \times (1/L) \times 100$$
$$\text{Result}_3 = (\{C_3 \times [V - (2 \times V_S)]\} + [(C_2 + C_1) \times V_S]) \times (1/L) \times 100$$
$$\text{Result}_4 = (\{C_4 \times [V - (3 \times V_S)]\} + [(C_3 + C_2 + C_1) \times V_S]) \times (1/L) \times 100$$

C_i = concentration of carbidopa or levodopa in the portion of sample withdrawn at time point *i* (mg/mL)
V = volume of the *Medium*, 900 mL
L = label claim of carbidopa or levodopa (mg/Tablet)
V_S = volume of the *Sample solution* withdrawn from the *Medium* (mL)

Tolerances: See *Table 6*.

Table 6

Time Point (*i*)	Time (h)	Amount Dissolved for Tablets That Contain 25 mg of Carbidopa and 100 mg of Levodopa (%)	Amount Dissolved for Tablets That Contain 50 mg of Carbidopa and 200 mg of Levodopa (%)
1	0.5	25–45	20–40
2	1	40–65	30–60
3	2.5	NLT 65	NLT 55
4	4	NLT 80	NLT 75

The percentages of the labeled amounts of carbidopa ($C_{10}H_{14}N_2O_4$) and levodopa ($C_9H_{11}NO_4$) dissolved at the times specified conform to *Dissolution* ⟨711⟩, *Acceptance Table 2*.

Test 6: If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 6*.

Medium: 0.1 N hydrochloric acid; 900 mL degassed under vacuum

Apparatus 1: 75 rpm

Times: 0.5, 1, 2.5, and 3.5 h

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

Mobile phase: To each liter of 12.5 g/L of monobasic sodium phosphate dihydrate, add 1.3 mL of *Solution A* and adjust with phosphoric acid to a pH of 2.8.

Standard solution: 0.03 mg/mL of USP Carbidopa RS and 0.11 mg/mL of USP Levodopa RS in *Medium*

Sample solution

For Tablets that contain 25 mg of carbidopa and 100 mg of levodopa: Pass a portion of the solution under test through a suitable filter of 0.45-µm pore size, discard the first 2 mL, and use the remaining filtrate. Use within 24 h.

For Tablets that contain 50 mg of carbidopa and 200 mg of levodopa: Pass a portion of the solution under test through a suitable filter of 0.45-µm pore size, discard the first 2 mL, and dilute with *Medium* (50:50). Use within 24 h.

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 3 times the retention time of levodopa
System suitability
Sample: *Standard solution*
[NOTE—The relative retention times for levodopa and carbidopa are 1.0 and 2.8, respectively.]
Suitability requirements
Resolution: NLT 2.0 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 concentration (C_i) of carbidopa ($C_{10}H_{14}N_2O_4$) or levodopa ($C_9H_{11}NO_4$) in the sample withdrawn from the vessel at each time point (*i*):

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

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)
D = dilution factor for the *Sample solution,* if needed

Calculate the percentage of the labeled amount of carbidopa ($C_{10}H_{14}N_2O_4$) or levodopa ($C_9H_{11}NO_4$) dissolved at each time point (*i*):

$$\text{Result}_1 = C_1 \times V \times (1/L) \times 100$$
$$\text{Result}_2 = \{[C_2 \times (V - V_S)] + (C_1 \times V_S)\} \times (1/L) \times 100$$
$$\text{Result}_3 = (\{C_3 \times [V - (2 \times V_S)]\} + [(C_2 + C_1) \times V_S]) \times (1/L) \times 100$$
$$\text{Result}_4 = (\{C_4 \times [V - (3 \times V_S)]\} + [(C_3 + C_2 + C_1) \times V_S]) \times (1/L) \times 100$$

C_i = concentration of carbidopa or levodopa in the portion of sample withdrawn at time point *i* (mg/mL)
V = volume of the *Medium*, 900 mL
L = label claim of carbidopa or levodopa (mg/Tablet)
V_S = volume of the *Sample solution* withdrawn from the *Medium* (mL)

Tolerances: See *Table 7*.

Table 7

Time Point (*i*)	Time (h)	Amount Dissolved for Tablets That Contain 25 mg of Carbidopa and 100 mg of Levodopa (%)	Amount Dissolved for Tablets That Contain 50 mg of Carbidopa and 200 mg of Levodopa (%)
1	0.5	15–40	10–30
2	1	35–60	25–50
3	2.5	NLT 70	NLT 65
4	3.5	NLT 85	NLT 80

The percentages of the labeled amounts of carbidopa ($C_{10}H_{14}N_2O_4$) and levodopa ($C_9H_{11}NO_4$) dissolved at the times specified conform to *Dissolution* ⟨711⟩, *Acceptance Table 2*.

▲**Test 7:** If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 7*.
Protect the analytical solutions from light.
Medium: 0.1 N hydrochloric acid VS; 900 mL
Apparatus 2: 50 rpm
Times: 0.5, 1, 1.5, and 4 h
Buffer: 6.0 g/L of anhydrous monobasic sodium phosphate in water adjusted with diluted phosphoric acid to a pH of 2.2
Mobile phase: Alcohol and *Buffer* (4:96)
Standard solution: (*L*/900) mg/mL each of USP Carbidopa RS and USP Levodopa RS prepared as follows, where *L* is the label claim, in mg/Tablet. Transfer suitable quantities of USP Carbidopa RS and USP Levodopa RS to an appropriate volumetric flask and add 70% of the flask volume of *Medium*. Sonicate to dissolve, and allow the solution to cool to room temperature. Dilute with *Medium* to volume.
Sample solution: Withdraw a 10-mL aliquot at each time point and pass a portion of the solution under test through a suitable filter. Replace the 10-mL aliquot withdrawn for analysis with a 10-mL aliquot of *Medium.*
Chromatographic system
(See *Chromatography* ⟨621⟩*, System Suitability*.)
Mode: LC
Detector: UV 280 nm
Column: 4.6-mm × 15-cm; 5-µm packing L1
Autosampler temperature: 6°
Flow rate: 1 mL/min
Injection volume: 20 µL
Run time: NLT 3 times the retention time of levodopa
System suitability
Sample: *Standard solution*
[NOTE—The relative retention times for levodopa and carbidopa are 1.0 and 1.9, respectively.]
Suitability requirements
Resolution: NLT 2.0 between levodopa and carbidopa
Tailing factor: NMT 1.5 for both carbidopa and levodopa
Relative standard deviation: NMT 1.0% for both carbidopa and levodopa
Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the concentration (C_i) of carbidopa ($C_{10}H_{14}N_2O_4$) or levodopa ($C_9H_{11}NO_4$) in the sample withdrawn from the vessel at each time point (*i*):

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

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)

Calculate the percentage of the labeled amount of carbidopa ($C_{10}H_{14}N_2O_4$) or levodopa ($C_9H_{11}NO_4$) dissolved at each time point (*i*):

$$\text{Result}_1 = C_1 \times V \times (1/L) \times 100$$
$$\text{Result}_2 = [(C_2 \times V) + (C_1 \times V_S)] \times (1/L) \times 100$$

$$\text{Result}_3 = \{(C_3 \times V) + [(C_2 + C_1) \times V_S]\} \times (1/L) \times 100$$
$$\text{Result}_4 = \{(C_4 \times V) + [(C_3 + C_2 + C_1) \times V_S]\} \times (1/L) \times 100$$

C_i = concentration of carbidopa or levodopa in the portion of sample withdrawn at time point i (mg/mL)
V = volume of the *Medium*, 900 mL
L = label claim of carbidopa or levodopa (mg/Tablet)
V_S = volume of the *Sample solution* withdrawn from the vessel and replaced with *Medium*, 10 mL

Tolerances: See *Table 8*.

Table 8

Time Point (*i*)	Time (h)	Amount of Carbidopa Dissolved (%)	Amount of Levodopa Dissolved (%)
1	0.5	15–35	15–35
2	1	30–60	30–60
3	1.5	50–80	50-80
4	4	NLT 80	NLT 80

The percentages of the labeled amount of carbidopa ($C_{10}H_{14}N_2O_4$) and levodopa ($C_9H_{11}NO_4$) dissolved at the times specified conform to *Dissolution* ⟨711⟩, *Acceptance Table 2*.▲ (TBD)

- **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.

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

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

System suitability solution: 1 µg/mL of USP Levodopa Related Compound B RS and 125 µg/mL of USP Carbidopa 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*

Sensitivity solution: 0.125 µg/mL of USP Carbidopa RS and 0.5 µg/mL of USP Levodopa RS in *Mobile phase* from the *Standard solution*

Sample solution: Nominally 0.125 mg/mL of carbidopa and nominally 0.5 mg/mL of levodopa in *Mobile phase* from NLT 10 finely powdered Tablets, prepared as follows. Transfer an accurately weighed portion of the powder into a suitable volumetric flask, dissolve in *Mobile phase*, and pass through a suitable filter.

Chromatographic system
(See *Chromatography* ⟨621⟩*, System Suitability*.)
Mode: LC
Detector: UV 280 nm
Column: 4.6-mm × 15-cm; 5-µm packing L1
Autosampler temperature: 6°
Flow rate: 1 mL/min
Injection volume: 20 µL
Run time: ▲NLT▲ 1S (USP41) 6 times the retention time of carbidopa

System suitability
Samples: *System suitability solution*, *Standard solution*, and *Sensitivity solution*
[NOTE—For the relative retention times, see ▲*Table 9*.]▲ (TBD)
Suitability requirements
Resolution: NLT 1.5 between carbidopa and levodopa related compound B, *System suitability solution*
Relative standard deviation: NMT 3.0% for both carbidopa and levodopa for five replicate injections, *Standard solution*
Signal-to-noise ratio: NLT 10 for carbidopa, *Sensitivity solution*

Analysis
Samples: *Standard solution* and *Sample solution*

Calculate the percentage of dihydroxybenzaldehyde, dihydroxyphenylacetone, and any unspecified carbidopa degradant 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 dihydroxybenzaldehyde, dihydroxyphenylacetone, or any unspecified carbidopa degradant 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* (mg/mL)
C_U = nominal concentration of carbidopa in the *Sample solution* (mg/mL)
F = relative response factor (see ▲*Table 9*)▲ (TBD)

Calculate the percentage of levodopa related compound A and any unspecified levodopa degradant 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 levodopa degradant 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 9*)▲ (TBD)

Acceptance criteria: See ▲*Table 9*.▲ (TBD)▲The reporting threshold is 0.05%, relative to the drug substance.▲ 1S (USP41)

▲Table 9▲ (TBD)

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Levodopa related compound A[a, b]	0.9	0.8	0.1
Levodopa	1.0	—	—
Methyldopa[c, d]	1.9	—	—
Levodopa related compound B[a, d]	2.1	—	—
Carbidopa	2.3	—	—
Dihydroxybenzaldehyde[c, e]	5.7	5.9	0.2

▲**Table 9**▲ (TBD) *(continued)*

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Dihydroxyphenylacetone[c, f]	6.3	1.0	1
3-*O*-Methylcarbidopa[d, g]	6.9	—	—
Any unspecified carbidopa degradant	—	1.0	0.2
Any unspecified levodopa degradant	—	1.0	0.1
Total degradants	—	—	4.0

[a] Individual impurity based on label claim of levodopa.
[▲b] 3-(2,4,5-Trihydroxyphenyl)-L-alanine.▲ (TBD)
[c] Individual impurity based on label claim of carbidopa.
[d] This impurity is listed for information only. It is monitored in the drug substance. This impurity is not to be reported and is not to be included in the total degradants.
[e] 3,4-Dihydroxybenzaldehyde.
[f] 3,4-Dihydroxyphenylacetone.
[g] (*S*)-2-Hydrazinyl-3-(4-hydroxy-3-methoxyphenyl)-2-methylpropanoic acid.

ADDITIONAL REQUIREMENTS

- **PACKAGING AND STORAGE:** Preserve in well-closed, light-resistant containers, and store at controlled room temperature.
- **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 Carbidopa RS
  USP Levodopa RS
  USP Levodopa Related Compound B RS
  3-Methoxytyrosine.
  $C_{10}H_{13}NO_4$ 211.21