Carbidopa and Levodopa Tablets

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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 Tablets monograph. The purpose for the revision is to add *Dissolution Test* 2 to accommodate drug products which were approved with different dissolution conditions and acceptance criteria. A *Labeling* section was also added.

- *Dissolution Test* 2 was validated using a µBondapak C18 brand of L1 column. The typical retention times for levodopa and carbidopa are about 2.8 and 6.8 min, respectively.

The Carbidopa and Levodopa Tablets Revision Bulletin supersedes the currently official monograph. The Revision Bulletin will be incorporated into the *Second Supplement* to *USP 40–NF 35*.

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

Carbidopa and Levodopa Tablets

DEFINITION

Carbidopa and Levodopa 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

Change to read:

- **A.**
  Diluent: 0.05 N hydrochloric acid and methanol (50:50)
  Standard solution A: 0.1 mg/mL of USP Carbidopa RS in *Diluent*
  Standard solution B: 0.1 mg/mL of USP Levodopa RS in *Diluent*
  Sample solution: Nominally 0.1 mg/mL of carbidopa from powdered Tablets in solution, prepared as follows. Transfer a portion of powdered Tablets to a suitable volumetric flask containing 50% of the final volume of 0.05 N hydrochloric acid. Agitate for 20 min. Add methanol to volume, and filter or centrifuge.
  Chromatographic system
  (See *Chromatography* ⟨621⟩, •*General Procedures,*• (RB 1-Feb-2017) *Thin-Layer Chromatography*.)
  Mode: TLC
  Adsorbent: 0.25-mm layer of chromatographic silica gel
  Application volume: 20 µL
  Developing solvent system: Acetone, chloroform, *n*-butanol, glacial acetic acid, and water (27.9: 18.6: 18.6: 18.6: 16.3)
  Spray reagent: 0.3 g of ninhydrin in 100 mL of *n*-butanol with 3 mL of glacial acetic acid
  Analysis
  Samples: *Standard solution A*, *Standard solution B*, and *Sample solution*
  Develop, using the *Developing solvent system,* until the solvent front has moved 15 cm. Air-dry, spray uniformly with 0.5 mL of *Spray reagent*, and heat at 105° for 10 min.
  Acceptance criteria: The *Sample solution* exhibits two spots (reddish brown for levodopa and yellow-orange for carbidopa) having R_F values that correspond to those exhibited by the *Standard solutions*.
- **B.** 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**
  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 final volume. Add 0.13% of the final 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. Pass through a membrane filter.
  Standard solution: 0.5 mg/mL of USP Levodopa RS and a quantity of USP Carbidopa RS, which is in a ratio with USP Levodopa RS that corresponds to the ratio of carbidopa to levodopa in the Tablets, in solution, prepared as follows. Transfer USP Levodopa RS and USP Carbidopa RS to a suitable volumetric flask, and dissolve in 0.1 N phosphoric acid, using 10% of the final volume. Warm gently to dissolve the Reference Standards, and dilute with water to volume.
  Sample solution: Nominally 0.5 mg/mL of levodopa from a suitable amount of powdered Tablets in solution, prepared as follows. Transfer a portion of fine powder from NLT 20 Tablets to a suitable volumetric flask. Add 10% of the final volume of 0.1 N phosphoric acid. Dilute with water to volume.
  Chromatographic system
  (See *Chromatography* ⟨621⟩, *System Suitability*.)
  Mode: LC
  Detector: UV 280 nm
  Column: 3.9-mm × 30-cm; packing L1
  Flow rate: 2 mL/min adjusted, as needed, to obtain retention times for levodopa and carbidopa of 4 min and 11 min, respectively
  Injection volume: 20 µL
  System suitability
  Sample: *Standard solution*
  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 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% 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**• (RB 1-Feb-2017)
  Medium: 0.1 N hydrochloric acid; 750 mL
  Apparatus 1: 50 rpm
  Time: 30 min
  Diluent, Mobile phase, Chromatographic system, and **System suitability:** Proceed as directed in the *Assay*.
  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 solution under test
  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 80% (*Q*) of the labeled amounts 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. Pass through a membrane filter.
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 amounts of carbidopa ($C_{10}H_{14}N_2O_4$) and levodopa ($C_9H_{11}NO_4$) are dissolved.● (RB 1-Feb-2017)

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

ADDITIONAL REQUIREMENTS

• **PACKAGING AND STORAGE:** Preserve in well-closed, light-resistant containers.

Add the following:

•• **LABELING:** The labeling states the *Dissolution* test used only if *Test 1* is not used.● (RB 1-Feb-2017)

• **USP REFERENCE STANDARDS ⟨11⟩**
USP Carbidopa RS
USP Levodopa RS