Carbidopa and Levodopa Orally Disintegrating Tablets

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Expert Committee Small Molecules 4

In accordance with the Rules and Procedures of the Council of Experts, the Small Molecules 4 Expert Committee has revised the Carbidopa and Levodopa Orally Disintegrating Tablets monograph. The purpose of this revision is to widen the Acceptance criteria for Methyldopa in the test for Organic Impurities from NMT 0.5% to NMT 0.6% to accommodate FDA-approved drug products with different limits. Additionally, the chemical information for USP Levodopa Related Compound A RS and USP Levodopa Related Compound B RS was updated to match the Reference Standard Certificate.

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

Should you have any questions, please contact Claire Chisolm, Senior Scientist II (301-230-3215 or cnc@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:
Result = \( \frac{r_U}{r_S} \times \frac{C_S}{C_U} \times 100 \)

- \( r_U \) = 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°C
- **Flow rate**: 2 mL/min
- **Injection volume**: 20 µL

System suitability
- **Sample**: Standard solution
- **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_{2}O_{4}) and levodopa (C_{9}H_{11}NO_{4}) dissolved:

\[
\text{Result} = \left( \frac{r_U}{r_S} \right) \times C_S \times V \times \left( \frac{1}{L} \right) \times 100
\]

\( r_U \) = peak response of carbidopa or levodopa from the Sample solution
\[ r_S = \text{peak response of carbidopa or levodopa from the Standard solution} \]
\[ C_S = \text{concentration of USP Carbidopa RS or USP Levodopa RS in the Standard solution (mg/mL)} \]
\[ V = \text{volume of the Medium, 750 mL} \]
\[ L = \text{label claim of carbidopa or levodopa (mg/Tablet)} \]

**Tolerances:** NLT 75% \((Q)\) of the labeled amount of carbidopa \((C_{10}H_{14}N_{2}O_{4})\) 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-\(\mu\)m 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 \(\times\) 30.0-cm; 10-\(\mu\)m packing L1

**Flow rate:** 2 mL/min

**Injection volume:** 20 \(\mu\)L

**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 \((\text{C}_{10}\text{H}_{14}\text{N}_{2}\text{O}_{4})\) and levodopa \((\text{C}_{9}\text{H}_{11}\text{NO}_{4})\) dissolved:

\[
\text{Result} = \left(\frac{r_u}{r_S}\right) \times C_S \times V \times \left(\frac{1}{L}\right) \times 100
\]

- \(r_u\) = 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 \((\text{C}_{10}\text{H}_{14}\text{N}_{2}\text{O}_{4})\) is dissolved, and NLT 75% \((Q)\) of the labeled amount of levodopa \((\text{C}_{9}\text{H}_{11}\text{NO}_{4})\) is dissolved.

**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:

\[
\text{Result} = \left( \frac{r_U}{r_S} \right) \times \left( \frac{C_S}{C_U} \right) \times \left( \frac{1}{F} \right) \times 100
\]

- \( r_U \) = 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:

\[
\text{Result} = \left( \frac{r_U}{r_S} \right) \times \left( \frac{C_S}{C_U} \right) \times \left( \frac{1}{F} \right) \times 100
\]

- \( r_U \) = 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

<table>
<thead>
<tr>
<th>Name</th>
<th>Relative Retention Time</th>
<th>Relative Response Factor</th>
<th>Acceptance Criteria, NMT (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Levodopa related compound A(a)</td>
<td>0.45</td>
<td>0.80</td>
<td>0.2</td>
</tr>
<tr>
<td>Levodopa</td>
<td>0.52</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Methyldopa(b)</td>
<td>0.84</td>
<td>1.0</td>
<td>▲0.6(\text{RB 1-May-2022})</td>
</tr>
</tbody>
</table>

\(a\) USP 308624-M4720-SM42020, rev. 00 20220429
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<tr>
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<th>Relative Retention Time</th>
<th>Relative Response Factor</th>
<th>Acceptance Criteria, NMT (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbidopa</td>
<td>1.0</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Levodopa related compound B&lt;sup&gt;c&lt;/sup&gt;</td>
<td>1.2</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>3-O-Methyl carbidopa&lt;sup&gt;e,d&lt;/sup&gt;</td>
<td>3.1</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>3,4-Dihydroxyphenylacetone&lt;sup&gt;b,d&lt;/sup&gt;</td>
<td>3.9</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Any individual unspecified degradation product&lt;sup&gt;e&lt;/sup&gt;</td>
<td>—</td>
<td>1.0</td>
<td>0.2</td>
</tr>
<tr>
<td>Total impurities&lt;sup&gt;e&lt;/sup&gt;</td>
<td>—</td>
<td>—</td>
<td>1.0</td>
</tr>
</tbody>
</table>

<sup>a</sup> Individual impurity based on the label claim of levodopa.

<sup>b</sup> Individual impurity based on the label claim of carbidopa.

<sup>c</sup> Process-related impurities, included for identification only; not to be included in total impurities.

<sup>d</sup> (S)-2-Hydrazinyl-3-(4-hydroxy-3-methoxyphenyl)-2-methylpropanoic acid.

<sup>e</sup> 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<sup>▲</sup> (RB 1-May-2022)
    - C₉H₁₁NO₅
    - 213.19
  - USP Levodopa Related Compound B RS
  - 3-Methoxytyrosine.
    - C₁₀H₁₃NO₄
    - 211.22<sup>▲</sup> (RB 1-May-2022)
  - USP Methyldopa RS
Not Applicable

Current DocID:

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