Bupropion Hydrochloride Extended-Release Tablets

**DEFINITION**
Bupropion Hydrochloride Extended-Release Tablets contain NLT 90.0% and NMT 110.0% of the labeled amount of bupropion hydrochloride (C_{13}H_{18}ClNO·HCl).

**IDENTIFICATION**
- **A. INFRARED ABSORPTION (197K)**
  
  **Sample:** Crush 1 Tablet using a mortar and pestle. Prepare an approximate 1% (w/w) dispersion of the sample in potassium bromide.
  
  **Acceptance criteria:** The Sample shows strong bands at about 1690, 1560, and 1240 cm⁻¹ and a weaker band at about 740 cm⁻¹, similar to the reference preparation.

- **B.** The retention time of the major peak of the Sample solution corresponds to that of the Standard solution, as obtained in the Assay.

**ASSAY**

**PROCEDURE**

**Diluent:** Methanol and 0.001 N hydrochloric acid (20:80)

**Solution A:** Acetonitrile, trifluoroacetic acid, and water (10:0.04:90)

**Solution B:** Acetonitrile, trifluoroacetic acid, and water (95:0.03:5)

**Mobile phase:** See Table 1.

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>Solution A (%)</th>
<th>Solution B (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>90</td>
<td>10</td>
</tr>
<tr>
<td>3.4</td>
<td>87</td>
<td>13</td>
</tr>
<tr>
<td>10.0</td>
<td>15</td>
<td>85</td>
</tr>
<tr>
<td>10.1</td>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td>13.0</td>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td>13.2</td>
<td>90</td>
<td>10</td>
</tr>
<tr>
<td>19.0</td>
<td>90</td>
<td>10</td>
</tr>
</tbody>
</table>

System suitability stock solution A: 0.02 mg/mL of USP Bupropion Hydrochloride Related Compound C and 0.2 mg/mL of USP Bupropion Hydrochloride Related Compound F in methanol

System suitability solution A: 0.0018 mg/mL of USP Bupropion Related Compound C and 0.018 mg/mL of USP Bupropion Related Compound F RS from System suitability stock solution A and Diluent

System suitability solution B: 0.09 mg/mL of m-chlorobenzoic acid in water

System suitability solution B: 0.0018 mg/mL of m-chlorobenzoic acid from System suitability stock solution B and Diluent

**Standard solution:** 0.6 mg/mL of USP Bupropion Hydrochloride RS in Diluent

**Sample solution:** Transfer a number of Tablets to a suitable homogenizer vessel containing sufficient methanol to obtain a concentration of 3.0 mg/mL of bupropion hydrochloride. Immediately homogenize the sample for 30 s at 20,000 rpm. Allow extraction for 3 min, and follow by two additional 10-s pulses, each at 20,000 rpm, pausing 3 min between these pulses to ensure complete extraction. Pass a portion of the solution through a nylon filter of 0.45-μm pore size, discarding the first 2–4 mL of the filtrate. Pipet 10.0 mL of the filtrate into a 50-mL volumetric flask, and add about 25 mL of 0.001 N hydrochloric acid. Allow to cool to room temperature, and dilute with 0.001 N hydrochloric acid to volume.

**Chromatographic system**

(See Chromatography (621), System Suitability.)

**Mode:** LC

**Detector:** UV 226 nm

**Column:** 4.6-mm × 10-cm; 3.5-μm packing L1

**Column temperature:** 40°

**Flow rate:** 1.5 mL/min

**Injection size:** 5 μL

**System suitability**

**Samples:** System suitability solution A, System suitability solution B, and Standard solution

**Suitability requirements**

**Resolution:** NLT 1.5, between bupropion hydrochloride related compound C and bupropion hydrochloride related compound F, System suitability solution A

**Tailing factor:** NMT 1.9, Standard solution

**Relative standard deviation:** NMT 1.5%, Standard solution

**Relative response factor:** Between 0.22 and 0.26 for m-chlorobenzoic acid. [NOTE—Use the responses from System suitability solution B and the Standard solution.]

**Analysis**

**Samples:** Standard solution and Sample solution

Calculate the percentage of the labeled amount of bupropion hydrochloride (C_{13}H_{18}ClNO·HCl) in the portion of Tablets taken:

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

- \(r_U\) = peak response for bupropion hydrochloride from the Sample solution
- \(r_S\) = peak response for bupropion hydrochloride from the Standard solution
- \(C_S\) = concentration of USP Bupropion Hydrochloride RS in the Standard solution (mg/mL)
- \(C_U\) = nominal concentration of bupropion hydrochloride in the Sample solution (mg/mL)

**Acceptance criteria:** 90.0%–110.0%

**PERFORMANCE TESTS**

**Change to read:**

- **DILUTION (711)**
  For products labeled for dosing every 12 h
  **Test 1**
  **Medium:** Water, 900 mL
  **Apparatus 2:** 50 rpm
  **Times:** 1, 4, and 8 h
  **Standard solution:** USP Bupropion Hydrochloride RS at a known concentration in Medium
  **Sample solution:** Pass a portion of the solution under test through a suitable filter, and dilute with Medium, if necessary.

**Instrumental conditions**

(See Spectrophotometry and Light-Scattering (851).)
2 Bupropion

Mode: UV-Vis
Analytical wavelength: 298 nm
Cell: 1.0 cm
Blank: Medium
Analysis: Samples: Standard solution and Sample solution
Tolerances: See Table 2.

Table 2

<table>
<thead>
<tr>
<th>Time (h)</th>
<th>Amount Dissolved (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>25–45</td>
</tr>
<tr>
<td>4</td>
<td>60–85</td>
</tr>
<tr>
<td>8</td>
<td>NLT 80</td>
</tr>
</tbody>
</table>

The percentages of the labeled amount of bupropion hydrochloride \((\text{C}_{13}\text{H}_{18}\text{ClNO} \cdot \text{HCl})\) dissolved at the times specified conform to Acceptance Table 2 in (711).

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, pH 1.5 (prepared by transferring 50 mL of concentrated hydrochloric acid to 6000 mL of water, adding 18 g of sodium hydroxide, mixing, and adjusting with either diluted sodium hydroxide or hydrochloric acid to a pH of 1.5 ± 0.05); 900 mL, deaerated

Apparatus 1: 50 rpm
Times: 1, 2, 4, and 6 h

Determine the percentages of the labeled amount of bupropion hydrochloride \((\text{C}_{13}\text{H}_{18}\text{ClNO} \cdot \text{HCl})\) dissolved by using the following method.

Buffer: 3.45 g of monobasic sodium phosphate monohydrate in 996 mL of water. Add 4.0 mL of triethylamine, and adjust with phosphoric acid to a pH of 2.80 ± 0.05.

Mobile phase: Methanol and Buffer (7:13)

Standard solution: USP Bupropion Hydrochloride RS in Medium at a known concentration similar to the one expected in the Sample solution

Sample solution: Use portions of the solution under test, and pass through a nylon filter of 0.45-µm pore size.

Chromatographic system
(See Chromatography (621), System Suitability.)

Mode: LC
Detector: UV 298 nm
Column: 4.6-mm x 15-cm; packing L1
Flow rate: 1 mL/min
Injection size: 20 µL

System suitability
Sample: Standard solution
Suitability requirements
Column efficiency: NLT 2000 theoretical plates
Tailing factor: NMT 2.0
Relative standard deviation: NMT 2.0%

Analysis
Samples: Standard solution and Sample solution
Tolerances: See Table 3.

Table 3

<table>
<thead>
<tr>
<th>Time (h)</th>
<th>Amount Dissolved (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>25–50</td>
</tr>
<tr>
<td>2</td>
<td>40–65</td>
</tr>
<tr>
<td>4</td>
<td>65–90</td>
</tr>
<tr>
<td>6</td>
<td>NLT 80</td>
</tr>
</tbody>
</table>

Table 4

<table>
<thead>
<tr>
<th>Time (h)</th>
<th>Amount Dissolved (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>30–55</td>
</tr>
<tr>
<td>2</td>
<td>50–75</td>
</tr>
<tr>
<td>4</td>
<td>70–90</td>
</tr>
<tr>
<td>6</td>
<td>NLT 80</td>
</tr>
</tbody>
</table>

The percentages of the labeled amount of bupropion hydrochloride \((\text{C}_{13}\text{H}_{18}\text{ClNO} \cdot \text{HCl})\) dissolved at the times specified conform to Acceptance Table 2 in (711).

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

Medium, Apparatus, Standard solution, Sample solution, Instrumental conditions, and Analysis: Proceed as directed for Test 1, except the wavelength is about 250 nm, and with wire coil sinkers, if necessary. Proceed as directed for Test 1, except to use a 0.5-cm cell.

Times: 1, 2, 4, and 6 h
Tolerances: See Table 5.

Table 5

<table>
<thead>
<tr>
<th>Time (h)</th>
<th>Amount Dissolved (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>35–55</td>
</tr>
<tr>
<td>3</td>
<td>65–85</td>
</tr>
<tr>
<td>6</td>
<td>NLT 80</td>
</tr>
</tbody>
</table>

The percentages of the labeled amount of bupropion hydrochloride \((\text{C}_{13}\text{H}_{18}\text{ClNO} \cdot \text{HCl})\) dissolved at the times specified conform to Acceptance Table 2 in (711).

Test 7: If the product complies with this test, the labeling indicates that it meets USP Dissolution Test 7.

Medium, Apparatus 1, and Times: Proceed as directed for Test 2, including the quantitative chromatographic method, but using as the Mobile phase a mixture of Buffer with methanol (55:45).

Tolerances: See Table 6.

Table 6

<table>
<thead>
<tr>
<th>Time (h)</th>
<th>Amount Dissolved (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>25–50</td>
</tr>
<tr>
<td>2</td>
<td>45–70</td>
</tr>
<tr>
<td>4</td>
<td>NLT 70</td>
</tr>
<tr>
<td>6</td>
<td>NLT 80</td>
</tr>
</tbody>
</table>

The percentages of the labeled amount of bupropion hydrochloride \((\text{C}_{13}\text{H}_{18}\text{ClNO} \cdot \text{HCl})\) dissolved at the times specified conform to Acceptance Table 2 in (711).

*Test 9: If the product complies with this test, the labeling indicates that it meets USP Dissolution Test 9.

Medium: 0.1 N hydrochloric acid, pH 1.5 (prepared as directed for Test 2); 900 mL
Apparatus 1: 50 rpm
Times: 1, 2, 4, and 8 h
Standard solution: \((L/1000)\) mg/mL of USP Bupropion hydrochloride RS inMedium, where \(L\) is the Tablet label claim, in mg.
Sample solution: Pass a portion of the solution under test through a suitable filter.
Instrumental conditions: Proceed as directed for Test 1.
Tolerances: See Table 7.

### Table 7

<table>
<thead>
<tr>
<th>Time (h)</th>
<th>Amount Dissolved (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>20-45</td>
</tr>
<tr>
<td>2</td>
<td>35-55</td>
</tr>
<tr>
<td>4</td>
<td>55-85</td>
</tr>
<tr>
<td>8</td>
<td>NLT 80</td>
</tr>
</tbody>
</table>

The percentages of the labeled amount of bupropion hydrochloride \((C_13H_18ClNO \cdot HCl)\) dissolved at the times specified conform to Acceptance Table 2 in (711).

For products labeled for dosing every 24 h

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, deaerated
- **Apparatus 1**: 75 rpm
- **Times**: 2, 4, 8, and 16 h
- **Standard solution**: USP Bupropion Hydrochloride RS at a known concentration inMedium
- **Sample solution**: Pass a portion of the solution under test through a suitable filter, and dilute with Medium, if necessary.
- **Instrumental conditions** (See Spectrophotometry and Light-Scattering (851).)
  - **Mode**: UV-Vis
  - **Analytical wavelength**: 252 nm
  - **Cell**: 1.0 cm
  - **Blank**: Medium
  - **Analysis Samples**: Standard solution and Sample solution
  - **Tolerances**: See Table 8.

### Table 8

<table>
<thead>
<tr>
<th>Time (h)</th>
<th>Amount Dissolved (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>NMT 20</td>
</tr>
<tr>
<td>4</td>
<td>20-45</td>
</tr>
<tr>
<td>8</td>
<td>65-90</td>
</tr>
<tr>
<td>16</td>
<td>NLT 80</td>
</tr>
</tbody>
</table>

The percentages of the labeled amount of bupropion hydrochloride \((C_13H_18ClNO \cdot HCl)\) dissolved at the times specified conform to Acceptance Table 2 in (711).• (IRA 3)

Test 6: If the product complies with this test, the labeling indicates that it meets USP Dissolution Test 6.
- **Medium and Apparatus**: Proceed as directed for Test 4.
- **Times**: 1, 2, 4, 8, and 12 h
- **Standard solution**: USP Bupropion Hydrochloride RS at a known concentration inMedium
- **Sample solution**: Pass a portion of the solution under test through a suitable filter, and dilute with Medium, if necessary.
- **Instrumental conditions** (See Spectrophotometry and Light-Scattering (851).)

### Table 9

<table>
<thead>
<tr>
<th>Time (h)</th>
<th>Amount Dissolved (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>15-35</td>
</tr>
<tr>
<td>2</td>
<td>25-50</td>
</tr>
<tr>
<td>4</td>
<td>40-65</td>
</tr>
<tr>
<td>8</td>
<td>65-90</td>
</tr>
<tr>
<td>12</td>
<td>NLT 80</td>
</tr>
</tbody>
</table>

The percentages of the labeled amount of bupropion hydrochloride \((C_13H_18ClNO \cdot HCl)\) dissolved at the times specified conform to Acceptance Table 2 in (711).

Test 8: If the product complies with this test, the labeling indicates that it meets USP Dissolution Test 8.
- **Medium**: 0.1 N hydrochloric acid; 900 mL
- **Apparatus 1**: 75 rpm
- **Times**: 2, 4, 8, and 16 h
- **Standard solution**
  - **For Tablets labeled to contain 150 mg**: USP Bupropion Hydrochloride RS dissolved inMedium (about 0.167 mg/mL)
  - **Apparatus 1**: 75 rpm
  - **Times**: 2, 4, 8, and 16 h
  - **Standard solution**: USP Bupropion Hydrochloride RS dissolved inMedium (about 0.333 mg/mL)
- **Sample solution**: Pass a portion of the solution under test through a suitable filter of 0.45-µm pore size.
- **Instrumental conditions** (See Spectrophotometry and Light-Scattering (851).)
  - **Mode**: UV-Vis
  - **Analytical wavelength**: 298 nm
  - **Blank**: Medium
  - **Tolerances**: See Table 10.

### Table 10

<table>
<thead>
<tr>
<th>Time (h)</th>
<th>Amount Dissolved (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>NMT 10</td>
</tr>
<tr>
<td>4</td>
<td>10-35</td>
</tr>
<tr>
<td>8</td>
<td>45-75</td>
</tr>
<tr>
<td>16</td>
<td>NLT 80</td>
</tr>
</tbody>
</table>

The percentages of the labeled amount of bupropion hydrochloride \((C_13H_18ClNO \cdot HCl)\) dissolved at the times specified conform to Acceptance Table 2 in (711).

**Uniformity of Dosage Units (905)**: Meet the requirements
- **Procedure for content uniformity**
  - **Standard solution**: 0.33 mg/mL of USP Bupropion Hydrochloride RS in water
  - **Sample solution**: Transfer 1 Tablet to a suitable homogenizer vessel containing a volume of water to obtain a concentration of about 0.33 mg of bupropion hydrochloride per mL. Immediately homogenize the sample using single 30-s pulses at 5,000, 10,000, and 15,000 rpm, and follow by two pulses each at 20,000 rpm. After the homogenate has settled, mix at 5000 rpm for an additional 30 s. Pass a portion of the solution through a nylon filter of 0.45-µm pore size, discarding the first 4 mL of the filtrate.
  - **Analysis**: Proceed as directed for the appropriate Dissolution procedure, using a 0.5-cm cell, and correct for dilution.

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**IMPURITIES**

- **Organic Impurities**


**Analysis**

**Samples:** Standard solution and Sample solution

Calculate the percentage of each impurity in the portion of Tablets taken:

\[
\text{Result} = \left( \frac{r_1}{r_0} \right) \times \left( \frac{C_s}{C_u} \right) \times F \times 100
\]

- \( r_0 \): peak response for each impurity from the Sample solution
- \( r_1 \): peak response for bupropion hydrochloride from the Standard solution
- \( C_s \): concentration of USP Bupropion Hydrochloride (mg/mL) in the Standard solution
- \( C_u \): nominal concentration of bupropion hydrochloride in the Sample solution (mg/mL)
- \( F \): relative response factor for each impurity (see Table 11 for values)

**Acceptance criteria:** See Table 11.

### Table 11 (Continued)

<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></td>
<td>100 mg or less</td>
<td>150 mg or greater</td>
<td></td>
</tr>
<tr>
<td>Bupropion</td>
<td>1.0</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Bupropion related compound F</td>
<td>1.71</td>
<td>0.55</td>
<td>1.2</td>
</tr>
<tr>
<td>Bupropion related compound C</td>
<td>1.75</td>
<td>0.59</td>
<td>0.3</td>
</tr>
<tr>
<td>m-Chlorobenzonic acid</td>
<td>1.80</td>
<td>0.24</td>
<td>0.3</td>
</tr>
<tr>
<td>1-(3-Chlorophenyl)-1,2-propanedione</td>
<td>2.25</td>
<td>1.00</td>
<td>0.4</td>
</tr>
<tr>
<td>Any unspecified impurity</td>
<td>—</td>
<td>1.00</td>
<td>0.2</td>
</tr>
<tr>
<td>Total impurities</td>
<td>—</td>
<td>—</td>
<td>3.2</td>
</tr>
<tr>
<td></td>
<td>—</td>
<td>—</td>
<td>3.3</td>
</tr>
</tbody>
</table>

### ADDITIONAL REQUIREMENTS

- **Packaging and Storage:** Preserve in well-closed containers.
- **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**
  - USP Bupropion Hydrochloride RS
  - USP Bupropion Hydrochloride Related Compound C RS
  - 1-(3-Chlorophenyl)-2-hydroxy-1-propanone. \( C_9H_9O_2Cl \) 184.62
  - USP Bupropion Hydrochloride Related Compound F RS
  - 1-(3-Chlorophenyl)-1-hydroxy-2-propanone. \( C_9H_9O_2 \) 184.62

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