

## Bupropion Hydrochloride Extended-Release Tablets

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<b>Expert Committee</b>	Chemical Medicines Monographs 4
<b>Reason for Revision</b>	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 Bupropion Hydrochloride Extended-Release Tablets monograph. The purpose for the revision is to add a *Dissolution Test* to accommodate a drug product which was approved with different dissolution conditions and acceptance criteria and to correct the cell length referenced in a dissolution test. Additionally, *Identification B* is updated to clarify that *Sample solution A* or *Sample solution B* may be used.

- *Dissolution Test 15* was validated using an Inertsil ODS-3V brand of L1 column. The typical retention time for bupropion is about 6.3 min.
- *Dissolution Test 8* was revised to specify a cell length of 0.5 cm instead of using the default path length of 1.0 cm from General Chapter <857>.

The Bupropion Hydrochloride Extended-Release Tablets Revision Bulletin supersedes the currently official monograph. The Revision Bulletin will be incorporated into the *First 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](mailto:hrj@usp.org)).

## 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 ( $C_{13}H_{18}ClNO \cdot HCl$ ).

### 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.

#### Change to read:

- **B.** The retention time of the major peak of **• Sample solution A** or **• Sample solution B** (RB 1-Aug-2016) corresponds to that of the *Standard solution*, as obtained in the *Assay*.

### ASSAY

#### Change to read:

#### • PROCEDURE

**Diluent 1:** 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 1

Time (min)	Solution A (%)	Solution B (%)
0	90	10
3.4	87	13
10.0	15	85
10.1	0	100
13.0	0	100
13.2	90	10
19.0	90	10

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

**System suitability solution:** 0.002 mg/mL of bupropion hydrochloride related compound C and 0.02 mg/mL of bupropion hydrochloride related compound F from the *System suitability stock solution* in *Diluent 1*

**Standard solution:** 0.6 mg/mL of USP Bupropion Hydrochloride RS in *Diluent 1*

**Sample stock solution A:** Transfer a number of Tablets, intact or crushed, to a suitable homogenizer vessel containing sufficient methanol to obtain a concentration of 3.0 mg/mL of bupropion hydrochloride. Imme-

diately 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- $\mu m$  pore size, discarding the first 2–4 mL of the filtrate.

**Sample solution A:** Nominally 0.6 mg/mL of bupropion hydrochloride from *Sample stock solution A* in 0.001 N hydrochloric acid

Alternatively, the *Sample solution* can be prepared as follows.

**Buffer:** Dissolve 100 g of **• anhydrous dibasic sodium phosphate** (RB 1-Aug-2016) in 1 L of water. Add 50 mL of phosphoric acid, stir or sonicate until dissolved, and mix. Adjust with phosphoric acid to a pH of 3.0.

**Diluent 2:** methanol and *Buffer* (20:80)

**Sample stock solution B:** Weigh and grind NLT 20 Tablets to prepare a solution having a nominal concentration of 3 mg/mL. Initially add *Diluent 2* (75% of the volume of the flask), stir for 30 min, and sonicate for 15 min. Dilute with *Diluent 2* to volume. Centrifuge a portion of the resulting solution, and use the supernatant.

**Sample solution B:** Nominally 0.6 mg/mL of bupropion hydrochloride from *Sample stock solution B* in *Diluent 2*

### Chromatographic system

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

**Mode:** LC

**Detector:** UV 226 nm

**Column:** 4.6-mm  $\times$  10-cm; 3.5- $\mu m$  packing L1

**Column temperature:** 40°

**Flow rate:** 1.5 mL/min

**Injection volume:** 5  $\mu L$

### System suitability

**Samples:** *System suitability solution* and *Standard solution*

[NOTE—See **• Table 17** (RB 1-Aug-2016) for the relative retention times.]

### Suitability requirements

**Resolution:** NLT 1.3 between bupropion hydrochloride related compound F and bupropion hydrochloride related compound C, *System suitability solution*

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

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

### Analysis

**Samples:** *Standard solution* and *Sample solution A* or *Sample solution B*

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

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times 100$$

$r_U$  = peak response of bupropion hydrochloride from *Sample solution A* or *Sample solution B*

$r_S$  = peak response of 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 *Sample solution A* or *Sample solution B* (mg/mL)

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Acceptance criteria: 90.0%–110.0%

### PERFORMANCE TESTS

#### Change to read:

#### • DISSOLUTION <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:** (L/900) mg/mL of USP Bupropion Hydrochloride RS in *Medium*, where L is the label claim, in mg/Tablet. Dilute with *Medium*, if necessary.

**Sample solution:** Pass a portion of the solution under test through a suitable filter, and dilute with *Medium*, if necessary.

##### Instrumental conditions

(See • *Ultraviolet-Visible Spectroscopy* <857> • (CN 1-May-2016).)

**Mode:** UV-Vis

**Analytical wavelength:** 298 nm

**Blank:** *Medium*

##### Analysis

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

Determine the percentages of the labeled amount of bupropion hydrochloride (C<sub>13</sub>H<sub>18</sub>ClNO · HCl) dissolved.

**Tolerances:** See *Table 2*.

**Table 2**

Time (h)	Amount Dissolved (%)
1	25–45
4	60–85
8	NLT 80

The percentages of the labeled amount of bupropion hydrochloride (C<sub>13</sub>H<sub>18</sub>ClNO · HCl) dissolved at the times specified conform to • *Dissolution* <711>, *Acceptance Table 2*. • (RB 1-Aug-2016)

**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 • hydrochloric acid • (RB 1-Aug-2016) 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); 900 mL, deaerated

**Apparatus 1:** 50 rpm

**Times:** 1, 2, 4, and 6 h

**Buffer:** 3.45 g of • monobasic sodium phosphate • (RB 1-Aug-2016) in 996 mL of water. Add 4.0 mL of triethylamine, and adjust with phosphoric acid to a pH of 2.80.

**Mobile phase:** Methanol and *Buffer* (35:65)

**Standard solution:** (L/900) mg/mL of USP Bupropion Hydrochloride RS in *Medium*, where L is the label claim, in mg/Tablet

**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 × 15-cm; packing L1

**Flow rate:** 1 mL/min

**Injection volume:** 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*

Determine the percentages of the labeled amount of bupropion hydrochloride (C<sub>13</sub>H<sub>18</sub>ClNO · HCl) dissolved.

**Tolerances:** See *Table 3*.

**Table 3**

Time (h)	Amount Dissolved (%)
1	25–50
2	40–65
4	65–90
6	NLT 80

The percentages of the labeled amount of bupropion hydrochloride (C<sub>13</sub>H<sub>18</sub>ClNO · HCl) dissolved at the times specified conform to • *Dissolution* <711>, *Acceptance Table 2*. • (RB 1-Aug-2016)

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

**Medium:** Water; 900 mL

**Apparatus 2:** 50 rpm. Use wire coil sinkers, if necessary.

**Times:** 1, 2, 4, and 6 h

**Standard solution:** (L/900) mg/mL of USP Bupropion Hydrochloride RS in *Medium*, where L is the label claim, in mg/Tablet. Dilute with *Medium*, if necessary.

**Sample solution:** Pass a portion of the solution under test through a suitable filter, and dilute with *Medium*, if necessary.

##### Instrumental conditions

(See • *Ultraviolet-Visible Spectroscopy* <857> • (CN 1-May-2016).)

**Mode:** UV-Vis

**Analytical wavelength:** 250 nm

**Blank:** *Medium*

##### Analysis

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

Determine the percentages of the labeled amount of bupropion hydrochloride (C<sub>13</sub>H<sub>18</sub>ClNO · HCl) dissolved.

**Tolerances:** See *Table 4*.

**Table 4**

Time (h)	Amount Dissolved (for Tablets that contain 200 mg of bupropion hydrochloride) (%)	Amount Dissolved (for Tablets that contain all other strengths of bupropion hydrochloride) (%)
1	30–50	30–55
2	45–65	50–75
4	65–85	70–90
6	NLT 78	NLT 80

The percentages of the labeled amount of bupropion hydrochloride (C<sub>13</sub>H<sub>18</sub>ClNO · HCl) dissolved at the times specified conform to • *Dissolution* (711), *Acceptance Table 2*. • (RB 1-Aug-2016)

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

**Medium:** Water; 900 mL

**Apparatus 2:** 50 rpm

**Times:** 1, 3, and 6 h

**Standard solution:** (L/900) mg/mL of USP Bupropion Hydrochloride RS in *Medium*, where L is the label claim, in mg/Tablet. Dilute with *Medium*, if necessary.

**Sample solution:** Pass a portion of the solution under test through a suitable filter, and dilute with *Medium*, if necessary.

**Instrumental conditions**

(See • *Ultraviolet-Visible Spectroscopy* (857) • (CN 1-May-2016).)

**Mode:** UV-Vis

**Analytical wavelength:** 298 nm

**Cell:** 0.5 cm

**Blank:** *Medium*

**Analysis**

**Samples:** *Standard solution* and *Sample solution*  
 Determine the percentages of the labeled amount of bupropion hydrochloride (C<sub>13</sub>H<sub>18</sub>ClNO · HCl) dissolved.

**Tolerances:** See *Table 5*.

**Table 5**

Time (h)	Amount Dissolved (%)
1	35–55
3	65–85
6	NLT 80

The percentages of the labeled amount of bupropion hydrochloride (C<sub>13</sub>H<sub>18</sub>ClNO · HCl) dissolved at the times specified conform to • *Dissolution* (711), *Acceptance Table 2*. • (RB 1-Aug-2016)

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

**Medium:** 0.1 N hydrochloric acid, pH 1.5 (prepared by transferring 50 mL of • hydrochloric acid • (RB 1-Aug-2016) 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); 900 mL, deaerated

**Apparatus 1:** 50 rpm

**Times:** 1, 2, 4, and 6 h

**Buffer:** 3.45 g of • monobasic sodium phosphate • (RB 1-Aug-2016) in 996 mL of water. Add 4.0 mL of triethylamine, and adjust with phosphoric acid to a pH of 2.80.

**Mobile phase:** Methanol and *Buffer* (45:55)

**Standard solution:** (L/900) mg/mL of USP Bupropion Hydrochloride RS in *Medium*, where L is the label claim, in mg/Tablet

**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 × 15-cm; packing L1

**Flow rate:** 1 mL/min

**Injection volume:** 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*  
 Determine the percentages of the labeled amount of bupropion hydrochloride (C<sub>13</sub>H<sub>18</sub>ClNO · HCl) dissolved.

**Tolerances:** See *Table 6*.

**Table 6**

Time (h)	Amount Dissolved (%)
1	25–50
2	45–70
4	NLT 70
6	NLT 80

The percentages of the labeled amount of bupropion hydrochloride (C<sub>13</sub>H<sub>18</sub>ClNO · HCl) dissolved at the times specified conform to • *Dissolution* (711), *Acceptance Table 2*. • (RB 1-Aug-2016)

**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 by transferring 50 mL of • hydrochloric acid • (RB 1-Aug-2016) 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); 900 mL

**Apparatus 1:** 50 rpm

**Times:** 1, 2, 4, and 8 h

**Standard solution:** (L/1000) mg/mL of USP Bupropion Hydrochloride 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.

**Instrumental conditions**

(See • *Ultraviolet-Visible Spectroscopy* (857) • (CN 1-May-2016).)

**Mode:** UV-Vis

**Analytical wavelength:** 298 nm

**Blank:** *Medium*

**Analysis**

**Samples:** *Standard solution* and *Sample solution*  
 Determine the percentages of the labeled amount of bupropion hydrochloride (C<sub>13</sub>H<sub>18</sub>ClNO · HCl) dissolved.

**Tolerances:** See *Table 7*.

**Table 7**

Time (h)	Amount Dissolved (%)
1	20–45
2	35–55
4	55–85
8	NLT 80

The percentages of the labeled amount of bupropion hydrochloride (C<sub>13</sub>H<sub>18</sub>ClNO · HCl) dissolved at the

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times specified conform to **Dissolution** <711>, **Acceptance Table 2**. (RB 1-Aug-2016)

**Test 10:** If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 10*.

**Medium:** Water; 900 mL

**Apparatus 2:** 50 rpm

**Times:** 1, 2, 4, and 8 h

**Standard solution:** (L/900) mg/mL of USP Bupropion Hydrochloride 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.

### Instrumental conditions

(See **Ultraviolet-Visible Spectroscopy** <857>. (CN 1-May-2016).)

**Mode:** UV-Vis

**Analytical wavelength:** 298 nm

**Cell:** 0.5 cm

**Blank:** *Medium*

### System suitability

**Sample:** *Standard solution*

### Suitability requirements

**Relative standard deviation:** NMT 2.0%

### Analysis

**Samples:** *Standard solution* and *Sample solution*  
Calculate the percentage of the labeled amount of bupropion hydrochloride (C<sub>13</sub>H<sub>18</sub>ClNO · HCl) dissolved at each time point (i):

$$\text{Result}_i = (A_i/A_5) \times C_5 \times V \times (1/L) \times 100$$

A<sub>i</sub> = absorbance of bupropion hydrochloride from the *Sample solution* at time point i

A<sub>5</sub> = absorbance of bupropion hydrochloride from the *Standard solution*

C<sub>5</sub> = concentration of USP Bupropion Hydrochloride RS in the *Standard solution* (mg/mL)

V = volume of *Medium*, 900 mL

L = label claim (mg/Tablet)

**Tolerances:** See *Table 8*.

**Table 8**

Time Point (i)	Time (h)	Amount Dissolved (%)
1	1	20–40
2	2	35–60
3	4	55–85
4	8	NLT 80

The percentages of the labeled amount of bupropion hydrochloride (C<sub>13</sub>H<sub>18</sub>ClNO · HCl) dissolved at the times specified conform to **Dissolution** <711>, **Acceptance Table 2**. (RB 1-Aug-2016)

### 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:** (L/900) mg/mL of USP Bupropion Hydrochloride RS in *Medium*, where L is the label claim, in mg/Tablet. Dilute with *Medium*, if necessary.

**Sample solution:** Pass a portion of the solution under test through a suitable filter, and dilute with *Medium*, if necessary.

### Instrumental conditions

(See **Ultraviolet-Visible Spectroscopy** <857>. (CN 1-May-2016).)

**Mode:** UV-Vis

**Analytical wavelength:** 252 nm

**Blank:** *Medium*

### Analysis

**Samples:** *Standard solution* and *Sample solution*  
Determine the percentages of the labeled amount of bupropion hydrochloride (C<sub>13</sub>H<sub>18</sub>ClNO · HCl) dissolved.

**Tolerances:** See *Table 9*.

**Table 9**

Time (h)	Amount Dissolved (%)
2	NMT 20
4	20–45
8	65–90
16	NLT 80

The percentages of the labeled amount of bupropion hydrochloride (C<sub>13</sub>H<sub>18</sub>ClNO · HCl) dissolved at the times specified conform to **Dissolution** <711>, **Acceptance Table 2**. (RB 1-Aug-2016)

**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, deaerated

**Apparatus 1:** 75 rpm

**Times:** 1, 2, 4, 8, and 12 h

**Standard solution:** (L/900) mg/mL of USP Bupropion Hydrochloride RS in *Medium*, where L is the label claim, in mg/Tablet. Dilute with *Medium*, if necessary.

**Sample solution:** Pass a portion of the solution under test through a suitable filter, and dilute with *Medium*, if necessary.

### Instrumental conditions

(See **Ultraviolet-Visible Spectroscopy** <857>. (CN 1-May-2016).)

**Mode:** UV-Vis

**Analytical wavelength:** 298 nm

**Blank:** *Medium*

### Analysis

**Samples:** *Standard solution* and *Sample solution*  
Determine the percentages of the labeled amount of bupropion hydrochloride (C<sub>13</sub>H<sub>18</sub>ClNO · HCl) dissolved.

**Tolerances:** See *Table 10*.

**Table 10**

Time (h)	Amount Dissolved (%)
1	15–35
2	25–50
4	40–65
8	65–90
12	NLT 80

The percentages of the labeled amount of bupropion hydrochloride (C<sub>13</sub>H<sub>18</sub>ClNO · HCl) dissolved at the times specified conform to **Dissolution** <711>, **Acceptance Table 2**. (RB 1-Aug-2016)

**Test 8:** If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 8*.

**Acid stage medium:** 0.1 N hydrochloric acid; 900 mL

**Buffer stage medium:** pH 6.8 phosphate buffer (RB 1-Aug-2016); 900 mL

**Apparatus 1:** 75 rpm

**Times:** 2 h in *Acid stage medium*; 3, 8, and 16 h in *Buffer stage medium*. The time in the *Buffer stage medium* includes the time in the *Acid stage medium*.

**Standard solution:** (L/900) mg/mL of USP Bupropion Hydrochloride RS in *Acid stage 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.

**Instrumental conditions**

(See **Ultraviolet-Visible Spectroscopy (857)** (CN 1-May-2016).)

**Mode:** UV-Vis

**Analytical wavelength:** 298 nm

**Cell:** 0.5 cm (RB 1-Aug-2016)

**Blank:** *Medium*

**Analysis**

**Samples:** *Standard solution* and *Sample solution*  
 Determine the percentages of the labeled amount of bupropion hydrochloride (C<sub>13</sub>H<sub>18</sub>ClNO · HCl) dissolved.

**Tolerances:** See *Table 11*.

**Table 11**

Time (h)	Amount Dissolved (%)
2	NMT 10
3	10–30
8	60–90
16	NLT 80

The percentages of the labeled amount of bupropion hydrochloride (C<sub>13</sub>H<sub>18</sub>ClNO · HCl) dissolved at the times specified conform to **Dissolution (711)**, *Acceptance Table 2*. (RB 1-Aug-2016)

**Test 11:** If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 11*.

**Acid stage medium:** 0.1 N hydrochloric acid; 750 mL

**Buffer stage medium:** pH 6.8 phosphate buffer (Add 250 mL of 76 g/L tribasic sodium phosphate (RB 1-Aug-2016) to the *Acid stage medium*, adjust with 2 N hydrochloric acid or 2 N sodium hydroxide to a pH of 6.8, if necessary.); 1000 mL

**Apparatus 2:** 50 rpm

**Times:** 2 h in *Acid stage medium*; 3, 8, and 16 h in *Buffer stage medium*. The time in the *Buffer stage medium* includes the time in the *Acid stage medium*.

**Acid stage standard solution:** 0.06 mg/mL of USP Bupropion Hydrochloride RS in *Acid stage medium*. Sonication may be used to aid in dissolution.

**Buffer stage standard solution:** 0.15 mg/mL of USP Bupropion Hydrochloride RS in *Buffer stage medium*. Sonication may be used to aid in dissolution.

**Sample solution:** Pass a portion of the solution under test through a suitable filter of 0.45-µm pore size.

**Instrumental conditions**

(See **Ultraviolet-Visible Spectroscopy (857)** (CN 1-May-2016).)

**Mode:** UV-Vis

**Analytical wavelength:** 298 nm

**Cell:** 0.5 cm

**Blank:** *Acid stage medium* or *Buffer stage medium*

**Analysis**

**Samples:** *Acid stage standard solution*, *Buffer stage standard solution*, and *Sample solution*

Calculate the concentration (C<sub>i</sub>) of bupropion hydrochloride (C<sub>13</sub>H<sub>18</sub>ClNO · HCl) in the sample withdrawn from the vessel at time point i:

$$\text{Result}_i = (A_i/A_s) \times C_s$$

A<sub>i</sub> = absorbance of bupropion hydrochloride from the *Sample solution* at time point i

A<sub>s</sub> = absorbance of bupropion hydrochloride from the *Acid stage standard solution* or *Buffer stage standard solution*

C<sub>s</sub> = concentration of USP Bupropion Hydrochloride RS in the *Acid stage standard solution* or *Buffer stage standard solution* (mg/mL)

Calculate the percentage of the labeled amount of bupropion hydrochloride (C<sub>13</sub>H<sub>18</sub>ClNO · HCl) dissolved at each time point (i):

$$\text{Result}_1 = C_1 \times V_A \times (1/L) \times 100$$

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

$$\text{Result}_3 = \{[C_3 \times (V_B - (2 \times V_S))] + [(C_2 + C_1) \times V_S]\} \times (1/L) \times 100$$

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

C<sub>i</sub> = concentration of bupropion hydrochloride in the portion of the sample withdrawn at time point i (mg/mL)

V<sub>A</sub> = volume of *Acid stage medium*, 750 mL

L = label claim (mg/Tablet)

V<sub>B</sub> = volume of *Buffer stage medium*, 1000 mL

V<sub>S</sub> = volume of *Sample solution* withdrawn from the *Acid stage medium* or *Buffer stage medium* (mL)

**Tolerances:** See *Table 12*.

**Table 12**

Time Point (i)	Time (h)	Amount Dissolved (%)
1	2	NMT 10
2	3	10–30
3	8	55–85
4	16	NLT 75

The percentages of the labeled amount of bupropion hydrochloride (C<sub>13</sub>H<sub>18</sub>ClNO · HCl) dissolved at the times specified conform to **Dissolution (711)**, *Acceptance Table 2*. (RB 1-Aug-2016)

**Test 12:** If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 12*.

**Medium:** 0.1 N hydrochloric acid; 900 mL

**Apparatus 1:** 75 rpm

**Times:** 2, 4, 8, and 12 h

**Standard solution:** (L/900) mg/mL of USP Bupropion Hydrochloride RS in *Medium*, where L is the label claim, in mg/Tablet

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**Sample solution:** Withdraw at least 10 mL of the solution under test and pass through a suitable filter.

**Instrumental conditions**

(See • *Ultraviolet-Visible Spectroscopy* <857>• (CN 1-May-2016).)

**Mode:** UV-Vis

**Analytical wavelength:** 252 nm

**Cell**

For Tablets labeled to contain 150 mg: 0.1 cm

For Tablets labeled to contain 300 mg: 0.05 cm

**Blank:** *Medium*

**System suitability**

**Sample:** *Standard solution*

**Suitability requirements**

**Relative standard deviation:** NMT 3.0%

**Analysis**

**Samples:** *Standard solution* and *Sample solution*  
Calculate the concentration ( $C_i$ ) of bupropion hydrochloride ( $C_{13}H_{18}ClNO \cdot HCl$ ) in the sample withdrawn from the vessel at time point  $i$ :

$$\text{Result}_i = (A_i/A_s) \times C_s$$

$A_i$  = absorbance of bupropion hydrochloride from the *Sample solution* at time point  $i$

$A_s$  = absorbance of bupropion hydrochloride from the *Standard solution*

$C_s$  = concentration of USP Bupropion Hydrochloride RS in the *Standard solution* (mg/mL)

Calculate the percentage of the labeled amount of bupropion hydrochloride ( $C_{13}H_{18}ClNO \cdot HCl$ ) dissolved at each time point ( $i$ ):

$$\text{Result}_1 = C_i \times V \times (1/L) \times 100$$

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

$$\text{Result}_3 = \{[C_3 \times [V - (2 \times V_s)]] + [(C_2 + C_1) \times V_s]\} \times (1/L) \times 100$$

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

$C_i$  = concentration of bupropion hydrochloride in the portion of the sample withdrawn at time point  $i$  (mg/mL)

$V$  = volume of *Medium*, 900 mL

$L$  = label claim (mg/Tablet)

$V_s$  = volume of *Sample solution* withdrawn from the *Medium* (mL)

**Tolerances:** See *Table 13*.

**Table 13**

Time Point ( $i$ )	Time (h)	Amount Dissolved (%)
1	2	NMT 25
2	4	25–50
3	8	60–85
4	12	NLT 80

The percentages of the labeled amount of bupropion hydrochloride ( $C_{13}H_{18}ClNO \cdot HCl$ ) dissolved at the times specified conform to • *Dissolution* <711>, *Acceptance Table 2*• (RB 1-Aug-2016)

**Test 13:** If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 13*.

**Medium:** 0.1 N hydrochloric acid; 900 mL, deaerated

**Apparatus 1:** 75 rpm

**Times:** 2, 4, 8, and 12 h

**Standard solution:** ( $L/900$ ) mg/mL of USP Bupropion Hydrochloride RS in *Medium*, where  $L$  is the label claim, in mg/Tablet

**Sample solution:** Withdraw at least 10 mL of the solution under test and centrifuge. Use the supernatant.

**Instrumental conditions**

(See • *Ultraviolet-Visible Spectroscopy* <857>• (CN 1-May-2016).)

**Mode:** UV-Vis

**Analytical wavelength:** 252 nm

**Cell:** 0.1 cm

**Blank:** *Medium*

**System suitability**

**Sample:** *Standard solution*

**Suitability requirements**

**Relative standard deviation:** NMT 2.0%

**Analysis**

**Samples:** *Standard solution* and *Sample solution*  
Calculate the concentration ( $C_i$ ) of bupropion hydrochloride ( $C_{13}H_{18}ClNO \cdot HCl$ ) in the sample withdrawn from the vessel at time point  $i$ :

$$\text{Result}_i = (A_i/A_s) \times C_s$$

$A_i$  = absorbance of bupropion hydrochloride from the *Sample solution* at time point  $i$

$A_s$  = absorbance of bupropion hydrochloride from the *Standard solution*

$C_s$  = concentration of USP Bupropion Hydrochloride RS in the *Standard solution* (mg/mL)

Calculate the percentage of the labeled amount of bupropion hydrochloride ( $C_{13}H_{18}ClNO \cdot HCl$ ) dissolved at each time point ( $i$ ):

$$\text{Result}_1 = C_i \times V \times (1/L) \times 100$$

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

$$\text{Result}_3 = \{[C_3 \times [V - (2 \times V_s)]] + [(C_2 + C_1) \times V_s]\} \times (1/L) \times 100$$

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

$C_i$  = concentration of bupropion hydrochloride in the portion of the sample withdrawn at time point  $i$  (mg/mL)

$V$  = volume of *Medium*, 900 mL

$L$  = label claim (mg/Tablet)

$V_s$  = volume of *Sample solution* withdrawn from the *Medium* (mL)

**Tolerances:** See *Table 14*.

**Table 14**

Time Point ( $i$ )	Time (h)	Amount Dissolved (150 mg/Tablet)(%)	Amount Dissolved (300 mg/Tablet)(%)
1	2	NMT 25	NMT 25
2	4	30–55	25–45
3	8	65–90	60–80
4	12	NLT 80	NLT 80

The percentages of the labeled amount of bupropion hydrochloride (C<sub>13</sub>H<sub>18</sub>ClNO · HCl) dissolved at the times specified conform to • *Dissolution* (711), *Acceptance Table 2*. • (RB 1-Aug-2016)

**Test 14:** If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 14*.

**Medium:** 0.1 N hydrochloric acid; 900 mL

**Apparatus 1:** 75 rpm

**Times:** 2, 4, 8, and 16 h

**Standard solution:** (L/900) mg/mL of USP Bupropion Hydrochloride RS in *Medium*, where L is the label claim, in mg/Tablet. If necessary, dilute the solution with *Medium*.

**Sample solution:** Pass a portion of the solution under test through a suitable filter. Replace the portion removed with the same volume of *Medium*. If necessary, dilute the filtrate with *Medium*.

**Instrumental conditions**

(See • *Ultraviolet-Visible Spectroscopy* (857) • (CN 1-May-2016).)

**Mode:** UV

**Analytical wavelength:** 252 nm

**Blank:** *Medium*

**Analysis**

**Samples:** *Standard solution* and *Sample solution*  
Calculate the concentration (C<sub>i</sub>) of bupropion hydrochloride (C<sub>13</sub>H<sub>18</sub>ClNO · HCl) in the sample withdrawn from the vessel at time point *i*:

$$\text{Result}_i = (A_i/A_s) \times C_s \times D$$

A<sub>i</sub> = absorbance from the *Sample solution* at time point *i*

A<sub>s</sub> = absorbance from the *Standard solution*

C<sub>s</sub> = concentration of USP Bupropion Hydrochloride RS in the *Standard solution* (mg/mL)

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

Calculate the percentage of the labeled amount of bupropion hydrochloride (C<sub>13</sub>H<sub>18</sub>ClNO · HCl) dissolved at each time point (*t*):

$$\text{Result}_1 = C_1 \times V \times (1/L) \times 100$$

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

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

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

C<sub>i</sub> = concentration of bupropion hydrochloride in the portion of the sample withdrawn at time point *i* (mg/mL)

V = volume of *Medium*, 900 mL

L = label claim (mg/Tablet)

V<sub>s</sub> = volume of *Sample solution* withdrawn at each time point and replaced with *Medium* (mL)

**Tolerances:** See *Table 15*.

**Table 15**

Time Point (i)	Time (h)	Amount Dissolved (%)
1	2	NMT 20
2	4	20–45

**Table 15 (Continued)**

Time Point (i)	Time (h)	Amount Dissolved (%)
3	8	55–85
4	16	NLT 80

The percentages of the labeled amount of bupropion hydrochloride (C<sub>13</sub>H<sub>18</sub>ClNO · HCl) dissolved at the times specified conform to • *Dissolution* (711), *Acceptance Table 2*.

**Test 15:** If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 15*.

**Acid stage**

**Acid stage medium:** 0.1 N hydrochloric acid, degassed; 900 mL

**Apparatus 1:** 100 rpm

**Time:** 2 h in *Acid stage medium*

**Buffer:** 3.5 g/L of monobasic sodium phosphate prepared as follows. Dissolve 3.45 g of monobasic sodium phosphate in 996 mL of water, add 4.0 mL of triethylamine, and adjust with phosphoric acid to a pH of 2.8.

**Mobile phase:** Methanol and *Buffer* (45:55)

**Acid stage standard solution:** 0.033 mg/mL of USP Bupropion Hydrochloride RS in *Acid stage medium*. Sonication may be used to promote dilution.

**Acid stage sample solution:** Pass a portion of the solution under test through a suitable filter, discard the first 5-mL, and use the filtrate. Then discard the Tablets and remaining solution. [NOTE—A 0.45-µm nylon membrane filter may be suitable.]

**Chromatographic system**

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

**Mode:** LC

**Detector:** UV 298 nm

**Column:** 4.6-mm × 15-cm; 5-µm packing L1

**Flow rate:** 1 mL/min

**Injection volume:** 10 µL

**Run time:** NLT 1.5 times the retention time of bupropion

**System suitability**

**Sample:** *Acid stage standard solution*

**Suitability requirements**

**Tailing factor:** NMT 2.0

**Relative standard deviation:** NMT 2.0%

**Analysis**

**Samples:** *Acid stage standard solution* and *Acid stage sample solution*

Calculate the percentage of the labeled amount of bupropion hydrochloride (C<sub>13</sub>H<sub>18</sub>ClNO · HCl) dissolved:

$$\text{Result} = (r_u/r_s) \times C_s \times V \times (1/L) \times 100$$

r<sub>u</sub> = peak response of bupropion from the *Acid stage sample solution*

r<sub>s</sub> = peak response of bupropion from the *Acid stage standard solution*

C<sub>s</sub> = concentration of USP Bupropion Hydrochloride RS in the *Acid stage standard solution* (mg/mL)

V = volume of *Acid stage medium*, 900 mL

L = label claim (mg/Tablet)

**Buffer stage:** Use fresh Tablets.

**Buffer stage medium:** pH 6.8 tribasic sodium phosphate buffer and 0.5% sodium lauryl sulfate (Dissolve 19 g of tribasic sodium phosphate in 1 L of water, add 7 mL of hydrochloric acid, and adjust with 0.2 N sodium hydroxide or dilute hydrochloric acid to a pH of 6.8. Add 5 g of sodium dodecyl

## 8 Bupropion

sulfate. To promote dissolution, the resulting solution can be continuously stirred and heated to 41°. Allow the solution to cool to 37° before use. Do not allow the temperature to fall below 36.5° before beginning the test.); 900 mL

**Apparatus 1:** 100 rpm

**Times:** 1, 2, 4, and 8 h

**Buffer:** 1.4 g/L of dibasic ammonium phosphate and 0.5 g/L of sodium 1-hexanesulfonate prepared as follows. Dissolve 1.4 g of dibasic ammonium phosphate and 0.5 g of sodium 1-hexanesulfonate in 1 L of water. To each 1 L of this solution, add 2.0 mL of triethylamine, and adjust with phosphoric acid to a pH of 7.0.

**Mobile phase:** Acetonitrile and Buffer (60:40)

**Buffer stage standard solution:** 0.33 mg/mL of USP Bupropion Hydrochloride RS in Buffer stage medium

**Buffer stage sample solution:** Pass a portion of the solution under test through a suitable filter, discard the first 5-mL, and use the filtrate.

**Chromatographic system:** Proceed as directed under the Acid stage

**System suitability**

**Sample:** Buffer stage standard solution

**Suitability requirements**

**Tailing factor:** NMT 2.0

**Relative standard deviation:** NMT 2.0%

**Analysis**

**Samples:** Buffer stage standard solution and Buffer stage sample solution

Calculate the concentration ( $C_i$ ) of bupropion hydrochloride ( $C_{13}H_{18}ClNO \cdot HCl$ ) in the sample withdrawn from the vessel at time point  $i$ :

$$\text{Result}_i = (r_i/r_s) \times C_s$$

- $r_i$  = peak response of bupropion from the Buffer stage sample solution at time point  $i$   
 $r_s$  = peak response of bupropion from the Buffer stage standard solution  
 $C_s$  = concentration of USP Bupropion Hydrochloride RS in the Buffer stage standard solution (mg/mL)

Calculate the percentage of the labeled amount of bupropion hydrochloride ( $C_{13}H_{18}ClNO \cdot HCl$ ) dissolved at each time point ( $i$ ):

$$\text{Result}_1 = C_1 \times V \times (1/L) \times 100$$

$$\text{Result}_2 = \{[C_2 \times (V - V_3)] + (C_1 \times V_3)\} \times (1/L) \times 100$$

$$\text{Result}_3 = \{[C_3 \times (V - 2 \times V_3)] + [(C_2 + C_1) \times V_3]\} \times (1/L) \times 100$$

$$\text{Result}_4 = \{[C_4 \times [V - (3 \times V_3)]] + [(C_3 + C_2 + C_1) \times V_3]\} \times (1/L) \times 100$$

- $C_i$  = concentration of bupropion hydrochloride in the portion of the sample withdrawn at time point  $i$  (mg/mL)  
 $V$  = volume of Buffer stage medium, 900 mL  
 $L$  = label claim (mg/Tablet)  
 $V_3$  = volume of Buffer stage sample solution withdrawn at each time point (mL)

**Tolerances:**

**Acid stage:** NMT 10%; The percentage of the labeled amount of bupropion hydrochloride ( $C_{13}H_{18}ClNO \cdot HCl$ ) dissolved at the time specified conforms to Dissolution <711>, Acceptance Table 3.

**Buffer stage:** See Table 16.

**Table 16**

Time Point (i)	Time (h)	Amount Dissolved (%)
1	1	5–25
2	2	25–45
3	4	60–85
4	8	NLT 85

The percentages of the labeled amount of bupropion hydrochloride ( $C_{13}H_{18}ClNO \cdot HCl$ ) dissolved at the times specified conform to Dissolution <711>, Acceptance Table 2. • (RB 1-Aug-2016)

- **UNIFORMITY OF DOSAGE UNITS (905):** Meet the requirements

### IMPURITIES

**Change to read:**

- **ORGANIC IMPURITIES**

**Diluent 1, Solution A, Solution B, Mobile phase, and Sample solution A or Sample solution B:** Proceed as directed in the Assay.

**System suitability stock solution A:** 0.02 mg/mL of USP Bupropion Hydrochloride Related Compound C RS, 0.02 mg/mL of USP Bupropion Hydrochloride Related Compound F RS, and 0.012 mg/mL of USP 3-Chlorobenzoic Acid RS in methanol

**System suitability solution A:** 0.002 mg/mL of bupropion hydrochloride related compound C, 0.002 mg/mL of bupropion hydrochloride related compound F, and 0.0012 mg/mL of 3-chlorobenzoic acid from System suitability stock solution A in Diluent 1

**System suitability stock solution B:** 0.012 mg/mL of USP 3-Chlorobenzoic Acid RS in methanol

**System suitability solution B:** 0.0012 mg/mL of 3-chlorobenzoic acid from System suitability stock solution B in Diluent 1

**Standard solution:** 0.0012 mg/mL of USP Bupropion Hydrochloride RS in Diluent 1

**Chromatographic system:** Proceed as directed in the Assay except use a Detector as follows:

**Detector:** UV 226 nm, adjusted  $\pm 2$  nm so that the relative response factor requirement is met. [NOTE—The peak responses of the compounds of interest are very sensitive to changes in the detection wavelength.]

**System suitability**

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

[NOTE—See Table 17 • (RB 1-Aug-2016) for the relative retention times.]

**Suitability requirements**

**Resolution:** NLT 1.3 between bupropion hydrochloride related compound F and bupropion hydrochloride related compound C, System suitability solution A; NLT 1.3 between bupropion hydrochloride C and 3-chlorobenzoic acid, System suitability solution A

**Relative standard deviation:** NMT 10%, Standard solution

**Relative response factor:** 3.8–4.5 for the peak response of 3-chlorobenzoic acid in System suitability solution B divided by the peak response from bupropion in the Standard solution

**Analysis**

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

Calculate the percentage of 3-chlorobenzoic acid in the portion of Tablets taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times 100$$

- $r_U$  = peak response of 3-chlorobenzoic acid from *Sample solution A* or *Sample solution B*
- $r_S$  = peak response of 3-chlorobenzoic acid from *System suitability solution B*
- $C_S$  = concentration of USP 3-Chlorobenzoic Acid RS in *System suitability solution B* (mg/mL)
- $C_U$  = nominal concentration of bupropion hydrochloride in *Sample solution A* or *Sample solution B* (mg/mL)

Calculate the percentage of each other degradation product 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 each other degradation product from *Sample solution A* or *Sample solution B*
- $r_S$  = peak response of 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 *Sample solution A* or *Sample solution B* (mg/mL)
- $F$  = relative response factor for each other degradation product (see **Table 17**)

Acceptance criteria: See **Table 17**.

**Table 17** (RB 1-Aug-2016) (Continued)

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)	
			100 mg or less	150 mg or greater
Bupropion	1.0	—	—	—
Bupropion related compound F	1.71	1.8	1.2	2.3
Bupropion related compound C	1.75	1.7	0.3	0.3
3-Chlorobenzoic acid	1.80	—	0.3	0.3
Bupropion dione derivative <sup>d</sup>	2.25	1.00	0.4	0.4
Any unspecified degradation product	—	1.00	0.2	0.2
Total impurities	—	—	3.2	3.3

<sup>a</sup> 2-Amino-1-(3-chlorophenyl)-1-propanone.

<sup>b</sup> (3*S*,5*S*,6*S*)-6-(3-Chlorophenyl)-6-hydroxy-5-methyl-3-thiomorpholine carboxylic acid.

<sup>c</sup> (3*S*,5*R*,6*R*)-6-(3-Chlorophenyl)-6-hydroxy-5-methyl-3-thiomorpholine carboxylic acid.

<sup>d</sup> 1-(3-Chlorophenyl)propane-1,2-dione.

**ADDITIONAL REQUIREMENTS**

- **PACKAGING AND STORAGE:** Preserve in well-closed containers. Store at controlled room temperature. Protect from light.
- **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 Bupropion Hydrochloride RS
  - USP Bupropion Hydrochloride Related Compound C RS  
1-(3-Chlorophenyl)-2-hydroxypropan-1-one.  
C<sub>9</sub>H<sub>9</sub>O<sub>2</sub>Cl 184.62
  - USP Bupropion Hydrochloride Related Compound F RS  
1-(3-Chlorophenyl)-1-hydroxypropan-2-one.  
C<sub>9</sub>H<sub>9</sub>O<sub>2</sub>Cl 184.62
  - USP 3-Chlorobenzoic Acid RS  
3-Chlorobenzoic acid.  
C<sub>7</sub>H<sub>5</sub>ClO<sub>2</sub> 156.57

**Table 17** (RB 1-Aug-2016)

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)	
			100 mg or less	150 mg or greater
Bupropion amine <sup>a</sup>	0.38	1.2	0.3	0.3
<i>S,S,S</i> -Thiomorpholine derivative <sup>b</sup>	0.56	1.1	1.0	1.5
<i>S,R,R</i> -Thiomorpholine derivative <sup>c</sup>	0.78	1.1	0.5	0.4

<sup>a</sup> 2-Amino-1-(3-chlorophenyl)-1-propanone.

<sup>b</sup> (3*S*,5*S*,6*S*)-6-(3-Chlorophenyl)-6-hydroxy-5-methyl-3-thiomorpholine carboxylic acid.

<sup>c</sup> (3*S*,5*R*,6*R*)-6-(3-Chlorophenyl)-6-hydroxy-5-methyl-3-thiomorpholine carboxylic acid.

<sup>d</sup> 1-(3-Chlorophenyl)propane-1,2-dione.