Bupropion Hydrochloride Extended-Release Tablets

Type of Posting	Revision Bulletin
Posting Date	29–Jul–2016
Official Date	1–Aug–2016
Expert Committee	Chemical Medicines Monographs 4
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 Bupropion Hydrochloride Extended-Release Tablets monograph. The purpose for the revision is to add a *Dissolution Tes*t 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).

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. 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.

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 × 10-cm; 3.5-µm packing L1

Column temperature: 40°

Flow rate: 1.5 mL/min

Injection volume: 5 µL

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)

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 ($C_{13}H_{18}ClNO \cdot HCl$) 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 ($C_{13}H_{18}ClNO \cdot HCl$) 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 ($C_{13}H_{18}ClNO \cdot HCl$) 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 ($C_{13}H_{18}ClNO \cdot HCl$) 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 ($C_{13}H_{18}ClNO \cdot HCl$) 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 ($C_{13}H_{18}ClNO \cdot HCl$) 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 ($C_{13}H_{18}ClNO \cdot HCl$) 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 ($C_{13}H_{18}ClNO \cdot HCl$) 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 ($C_{13}H_{18}ClNO \cdot HCl$) 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 ($C_{13}H_{18}ClNO \cdot HCl$) 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 ($C_{13}H_{18}ClNO \cdot HCl$) 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 ($C_{13}H_{18}ClNO \cdot HCl$) dissolved at the

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 ($C_{13}H_{18}ClNO \cdot HCl$) dissolved at each time point (*i*):

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

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)
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 ($C_{13}H_{18}ClNO \cdot HCl$) 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 ($C_{13}H_{18}ClNO \cdot HCl$) 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 ($C_{13}H_{18}ClNO \cdot HCl$) 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 ($C_{13}H_{18}ClNO \cdot HCl$) 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 ($C_{13}H_{18}ClNO \cdot HCl$) 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 ($C_{13}H_{18}ClNO \cdot HCl$) 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 ($C_{13}H_{18}ClNO \cdot HCl$) 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_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 *Acid stage standard solution* or *Buffer stage standard solution*
C_S = 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 ($C_{13}H_{18}ClNO \cdot HCl$) 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_i = concentration of bupropion hydrochloride in the portion of the sample withdrawn at time point *i* (mg/mL)
V_A = volume of *Acid stage medium*, 750 mL
L = label claim (mg/Tablet)
V_B = volume of *Buffer stage medium*, 1000 mL
V_S = 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 ($C_{13}H_{18}ClNO \cdot HCl$) 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

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*):

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

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

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

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

C_i = concentration of 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*):

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

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

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

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

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

$$\text{Result}_i = (A_i/A_S) \times C_S \times D$$

A_i = absorbance from the *Sample solution* at time point *i*
A_S = absorbance from the *Standard solution*
C_S = 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 ($C_{13}H_{18}ClNO \cdot HCl$) dissolved at each time point (*i*):

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

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

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

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

C_i = concentration of 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 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
3	8	55–85
4	16	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*.

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: 10µL
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 ($C_{13}H_{18}ClNO \cdot HCl$) dissolved:

$$\text{Result} = (r_U/r_S) \times C_S \times V \times (1/L) \times 100$$

r_U = peak response of bupropion from the *Acid stage sample solution*
r_S = peak response of bupropion from the *Acid stage standard solution*
C_S = 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

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*):

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

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

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

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

C_i = concentration of bupropion hydrochloride in the portion of the sample withdrawn at time point *i* (mg/mL)
V = volume of *Buffer stage medium*, 900 mL
L = label claim (mg/Tablet)
V_S = 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 ±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*. (RB 1-Aug-2016))

Acceptance criteria: See *Table 17*. (RB 1-Aug-2016)

Table 17 (RB 1-Aug-2016)

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%) 100 mg or less	Acceptance Criteria, NMT (%) 150 mg or greater
Bupropion amine[a]	0.38	1.2	0.3	0.3
S,S,S-Thiomorpholine derivative[b]	0.56	1.1	1.0	1.5
S,R,R,-Thiomorpholine derivative[c]	0.78	1.1	0.5	0.4
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[d]	2.25	1.00	0.4	0.4
Any unspecified degradation product	—	1.00	0.2	0.2
Total impurities	—	—	3.2	3.3

[a] 2-Amino-1-(3-chlorophenyl)-1-propanone.
[b] (3*S*,5*S*,6*S*)-6-(3-Chlorophenyl)-6-hydroxy-5-methyl-3-thiomorpholine carboxylic acid.
[c] (3*S*,5*R*,6*R*)-6-(3-Chlorophenyl)-6-hydroxy-5-methyl-3-thiomorpholine carboxylic acid.
[d] 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.
  $C_9H_9O_2Cl$ 184.62
  USP Bupropion Hydrochloride Related Compound F RS
  1-(3-Chlorophenyl)-1-hydroxypropan-2-one.
  $C_9H_9O_2Cl$ 184.62
  USP 3-Chlorobenzoic Acid RS
  3-Chlorobenzoic acid.
  $C_7H_5ClO_2$ 156.57