Verapamil Hydrochloride Extended-Release Tablets

DEFINITION

Verapamil Hydrochloride Extended-Release Tablets contain NLT 90.0% and NMT 110.0% of the labeled amount of verapamil hydrochloride ($C_{27}H_{38}N_2O_4 \cdot HCl$).

IDENTIFICATION

• **A. INFRARED ABSORPTION ⟨197F⟩**

Standard: 1.92 mg/mL of USP Verapamil Hydrochloride RS in water. Transfer 25 mL of this solution to a 125-mL separatory funnel. Add 2 mL of 1 N sodium hydroxide, and extract with 25 mL of chloroform, shaking for 2 min. Pass the chloroform extract through a filter containing anhydrous sodium sulfate, and collect the filtrate in a porcelain dish. Rinse with an additional 10 mL of chloroform, collecting the rinsing in the same porcelain dish. Evaporate on a steam bath with the aid of a current of air to dryness, and dry the oily residue at 105° for 30 min.

Sample: Nominally 1.2 mg/mL of verapamil hydrochloride in 50 mM hydrochloric acid prepared as follows. Crush 1 Tablet, and transfer the powder to a volumetric flask of suitable size. Add 50 mM hydrochloric acid to about 75% of the final volume, and dissolve by heating, with stirring, for 40 min. Cool, and dilute with 50 mM hydrochloric acid to volume. Filter, and transfer 40 mL of the filtrate to a 125-mL separatory funnel. Add 4 mL of 1 N sodium hydroxide, and extract with 20 mL of chloroform, shaking for 2 min. Pass the chloroform extract through a filter containing anhydrous sodium sulfate, and collect the filtrate in a porcelain dish. Rinse with an additional 10 mL of chloroform, collecting the rinsing in the same porcelain dish. Evaporate on a steam bath with the aid of a current of air to dryness, and dry the oily residue at 105° for 30 min.

Acceptance criteria: Meet the requirements

ASSAY

• **PROCEDURE**

Buffer: To 0.82 g of sodium acetate add 33 mL of glacial acetic acid, and dilute with water to 1 L.

Mobile phase: Acetonitrile, 2-aminoheptane, and *Buffer* (60:1:140)

System suitability solution: 2.5 mg/mL of USP Verapamil Hydrochloride RS and 2.0 mg/mL of USP Verapamil Related Compound B RS in *Mobile phase*

Standard solution: 1.2 mg/mL of USP Verapamil Hydrochloride RS in *Mobile phase*

Sample solution: Transfer an equivalent to 240 mg of verapamil hydrochloride, from powdered Tablets (NLT 20), to a 200-mL volumetric flask, and add about 160 mL of *Mobile phase*. Sonicate for 15 min, stir for 15 min, dilute with *Mobile phase* to volume, and mix. Centrifuge a portion for 20 min, and use the supernatant as the *Sample solution*.

Chromatographic system
(See *Chromatography* ⟨621⟩, *System Suitability*.)
Mode: LC
Detector: UV 278 nm
Column: 4.6-mm × 15-cm; packing L1
Flow rate: 1 mL/min
Injection volume: 10 µL

System suitability
Samples: *System suitability solution* and *Standard solution*
Suitability requirements
Resolution: NLT 1.5 between verapamil and verapamil related compound B, *System suitability solution*
Relative standard deviation: NMT 2.0%, *Standard solution*

Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the percentage of the labeled amount of verapamil hydrochloride ($C_{27}H_{38}N_2O_4 \cdot HCl$) in the portion of Tablets taken:

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

r_U = peak response from the *Sample solution*
r_S = peak response from the *Standard solution*
C_S = concentration of USP Verapamil Hydrochloride RS in the *Standard solution* (mg/mL)
C_U = nominal concentration of verapamil hydrochloride in the *Sample solution* (mg/mL)

Acceptance criteria: 90.0%–110.0%

PERFORMANCE TESTS

Change to read:

• **DISSOLUTION ⟨711⟩**

Test 1: If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 1*. Proceed as directed for *Apparatus 1* and *Apparatus 2, Delayed-Release Dosage Forms, Method B, Procedure*.

Acid stage: Using 900 mL of simulated gastric fluid TS (without enzyme), conduct this stage of the test for 1 h.

Buffer stage: Using 900 mL of simulated intestinal fluid TS (without enzyme), conduct this stage of the test for 7 h.

Apparatus 2: 50 rpm

Times
Acid stage: 1 h
Buffer stage: 2, 3.5, 5, and 8 h

Standard solution: USP Verapamil Hydrochloride RS in 0.01 N hydrochloric acid

Sample solution: Pass portions of the solution under test through a suitable filter. Dilute with *Medium* as necessary.

Blank solution: 0.01 N hydrochloric acid

Analysis: Wrap each Tablet in a wire helix to prevent the Tablets from floating. After 1 h in the *Acid stage*, withdraw a specimen for analysis, and carefully transfer the dosage form, including the wire helix, to a vessel containing the *Buffer stage* medium, which has been previously warmed to 37 ± 0.5°. Pass a portion of the solution under test at each time interval using a suitable glass microfiber filter paper. Dilute, if necessary, the filtered portions of the solutions under test with water at the 1-h interval and with 0.1 N hydrochloric acid at the 2-, 3.5-, 5-, and 8-h intervals. Determine the percentage of the labeled amount of verapamil hydrochloride dissolved.

[NOTE—Use only filters that have been shown not to absorb verapamil.]

Detector: UV 278 nm
Tolerances: See *Table 1* and *Table 2*.

Table 1. For Products Labeled to Contain 180 or 240 mg

Time (h)	Amount Dissolved
1	7%–15%
2	16%–30%
3.5	31%–50%
5	51%–75%
8	NLT 85%

Table 2. For Products Labeled to Contain 120 mg

Time (h)	Amount Dissolved
1	10%–21%
2	18%–33%
3.5	35%–60%
5	50%–82%
8	NLT 85%

The percentages of the labeled amount of verapamil hydrochloride dissolved at the times specified conform to *Acceptance Table 2* in *Dissolution* ⟨711⟩.

Test 2: If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 2*. Proceed as directed for *Test 1*, except that in *Analysis*, the Tablet is not required to be wrapped in a wire helix.
Tolerances: See *Table 3*, *Table 4*, and *Table 5*.

Table 3. For Products Labeled to Contain 240 mg

Time (h)	Amount Dissolved
1	8%–20%
2	15%–35%
3.5	35%–65%
5	55%–85%
8	NLT 80%

Table 4. For Products Labeled to Contain 180 mg

Time (h)	Amount Dissolved
1	10%–25%
2	20%–40%
3.5	40%–75%
8	NLT 80%

Table 5. For Products Labeled to Contain 120 mg

Time (h)	Amount Dissolved
1	10%–25%
2	20%–40%
3.5	35%–70%
5	55%–85%
8	NLT 80%

The percentages of the labeled amount of verapamil hydrochloride dissolved at the times specified conform to *Acceptance Table 2* in *Dissolution* ⟨711⟩.

Test 3: If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 3*. Proceed as directed for *Test 1*.
Tolerances: See *Table 6*.

Table 6

Time (h)	Amount Dissolved
1	8%–20%
2	15%–35%
3.5	27%–57%
5	45%–75%
8	NLT 80%

The percentages of the labeled amount of verapamil hydrochloride dissolved at the times specified conform to *Acceptance Table 2* in *Dissolution* ⟨711⟩.

Test 4: If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 4*.
Medium: Simulated intestinal fluid TS (without enzyme); 50 mL
Apparatus 7: 20 cycles/min (see *Drug Release* ⟨724⟩)
Detector: UV 278 nm
Standard solution: USP Verapamil Hydrochloride RS in *Medium*
Analysis: Scrape about 2 mm × 2 mm of the coating from the side edge of the Tablet under test. Glue the system to a plastic rod sample holder at the area where the color has been removed. Attach each plastic sample holder to an arm of the apparatus, which reciprocates at an amplitude of about 2 cm and 15–30 cycles/min. The Tablet is continuously immersed in tubes containing 50 mL of *Medium* at 37°. At the end of each specified test interval, the systems are transferred to the next row of new test tubes containing 50 mL of fresh *Medium*. Remove the tubes after the last test interval, and allow them to cool to room temperature. Add 2.0 mL of 1.0 M phosphoric acid to each tube, and dilute with water to 50 mL. Stir and mix each tube thoroughly. Determine the percentages of the labeled amount of verapamil hydrochloride for the filtered portions of the solution under test, suitably diluted with *Medium*.
Tolerances: See *Table 7*.

Table 7

Time (h)	Amount Dissolved
3	NMT 10%
6	20%–50%
9	52.5%–82.5%
14	NLT 85%

The percentages of the labeled amount of verapamil hydrochloride dissolved at the times specified conform to *Acceptance Table 2* in *Dissolution* ⟨711⟩.

Test 5: If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 5*.
Phosphate buffer: Dissolve 6.8 g of monobasic potassium phosphate in 250 mL of water. Add 190 mL of 0.2 N sodium hydroxide in 400 mL of water, adjust with 0.2 N sodium hydroxide to a pH of 7.5 ± 0.1, and dilute with water to 1000 mL.
Medium: *Phosphate buffer*; 900 mL
Apparatus 2: 50 rpm
Detector: UV 278 nm
Standard solution: USP Verapamil Hydrochloride RS in *Medium*

Sample solution: Pass portions of the solution under test through a suitable filter. Dilute with *Medium* as necessary.
Analysis: Determine the percentage of the labeled amount of verapamil hydrochloride ($C_{27}H_{38}N_2O_4 \cdot HCl$) dissolved.
Tolerances: See *Table 8*.

Table 8

Time (h)	Amount Dissolved
1	2%–12%
2	10%–25%
4	25%–50%
8	NLT 80%

The percentages of the labeled amount of verapamil hydrochloride dissolved at the times specified conform to *Acceptance Table 2* in *Dissolution* ⟨711⟩.

•**Test 6:** If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 6*.
Acid stage, Buffer stage, Apparatus, Times, and **Detector:** Proceed as directed for *Test 1*.
Standard solution: 0.04 mg/mL of USP Verapamil Hydrochloride RS in 0.01 N hydrochloric acid
Sample solution: Pass portions of the solution under test through a suitable filter. Dilute with 0.1 N hydrochloric acid to prepare a sample of concentration similar to that of the *Standard solution*.
Analysis
Samples: *Standard solution* and *Sample solution*
Proceed as directed for *Test 1*. Calculate the concentration, C_i, of verapamil hydrochloride dissolved in *Medium* (mg/mL) at each time point *i*:

$$C_i = (A_U/A_S) \times C_S \times D$$

A_U = absorbance of verapamil from the *Sample solution*
A_S = absorbance of verapamil from the *Standard solution*
C_S = concentration of USP Verapamil Hydrochloride RS in the *Standard solution* (mg/mL)
D = dilution factor

Calculate the percentage of the labeled amount of verapamil hydrochloride ($C_{27}H_{38}N_2O_4 \cdot HCl$) dissolved ($Q_i$), at each time point *i*:

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

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

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

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

$$\text{Result}_5 = \{[C_5 \times (V - (4 \times V_S))] + [(C_4 + C_3 + C_2 + C_1) \times V_S]\} \times (1/L) \times 100$$

C_i = concentration of verapamil hydrochloride in the portion of sample withdrawn at time point *i* (mg/mL)
V = volume of *Medium*, 900 mL
V_S = volume of the *Sample solution* withdrawn at each time point from the *Medium* in the *Buffer stage* (mL)
L = label claim (mg/Tablet)

Tolerances: See *Table 9*.

Table 9

Time point (*i*)	Time (h)	Amount Dissolved (%)		
		Tablet Strength—240 mg	Tablet Strength—180 mg	Tablet Strength—120 mg
1	1	10–25	10–25	15–30
2	2	25–45	27–47	35–55
3	3.5	50–75	55–80	60–85
4	4	70–90	NLT 75	NLT 80
5	8	NLT 85	NLT 85	NLT 85

The percentages of the labeled amount of verapamil hydrochloride dissolved at the times specified conform to *Acceptance Table 2* in *Dissolution* ⟨711⟩.• (RB 1-Feb-2013)

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

IMPURITIES

• **ORGANIC IMPURITIES**
Buffer, Mobile phase, System suitability solution, Standard solution, Sample solution, Chromatographic system, and **System suitability:** Proceed as directed in the *Assay*.
Analysis
Sample: *Sample solution*
Calculate the percentage of each impurity in the portion of Tablets taken:

$$\text{Result} = (r_U/r_T) \times 100$$

r_U = peak response for each impurity from the *Sample solution*
r_T = sum of the responses for all peaks from the *Sample solution*

Acceptance criteria
Individual impurities: NMT 0.5%
Total impurities: NMT 1.0%

ADDITIONAL REQUIREMENTS

• **PACKAGING AND STORAGE:** Preserve in tight, light-resistant containers.
• **LABELING:** The labeling indicates the *Dissolution Test* with which the product complies.
• **USP REFERENCE STANDARDS ⟨11⟩**
USP Verapamil Hydrochloride RS
USP Verapamil Related Compound B RS
Benzeneacetonitrile, α-[2-[[2-(3,4-dimethoxyphenyl)-ethyl]methylamino]ethyl]-3,4-dimethoxy-α-(1-methylethyl)-, monohydrochloride.
$C_{26}H_{36}N_2O_4 \cdot HCl$ 477.05