Status: Currently Official on 17-Feb-2025
Official Date: Official as of 01-Aug-2018
Document Type: USP Monographs
DocId: GUID-42ECE4EC-BB14-49CB-A2A5-A813E0B42364_5_en-US
DOI: https://doi.org/10.31003/USPNF_M88099_05_01
DOI Ref: cqd0p

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

• **B.** The UV spectrum of the major peak of the *Diluted sample solution* corresponds to that of the *Diluted standard solution*, as obtained in the *Assay*.

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*

Diluted standard solution: 0.6 mg/mL of USP Verapamil Hydrochloride RS in *Mobile phase* from the *Standard solution*

Sample solution: Nominally 1.2 mg/mL of verapamil hydrochloride from Tablets prepared as follows. Transfer an amount equivalent to 240 mg of verapamil hydrochloride, from NLT 20 powdered Tablets, 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.

Diluted sample solution: Nominally 0.6 mg/mL of verapamil hydrochloride in *Mobile phase* from the *Sample solution*

Chromatographic system

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

Mode: LC

Detector: UV 278 nm. For *Identification B*, use a diode array detector in the range of 200–400 nm.

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

Flow rate: 1 mL/min

Injection volume: 10 µL

Run time: NLT 3 times the retention time of verapamil

System suitability

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

[Note—The relative retention times for verapamil related compound B and verapamil are 0.85 and 1.0, respectively.]

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*, *Diluted standard solution*, *Sample solution*, and *Diluted sample solution*

[Note—The *Diluted standard solution* and *Diluted sample solution* are used for *Identification B*.]

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 of verapamil from the *Sample solution*

r_S = peak response of verapamil 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

• **Dissolution** ⟨711⟩

Test 1: If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 1*. Proceed as directed in *Dissolution ⟨711⟩, Procedure, Apparatus 1 and Apparatus 2, Delayed-Release Dosage Forms, Method B Procedure*.

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

Buffer stage medium: 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 stagemedium,* 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°. At each time interval, pass a portion of the solution under test through 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 ($C_{27}H_{38}N_2O_4 \cdot HCl$) 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

Time (h)	Amount Dissolved (%)
8	NLT 85

The percentages of the labeled amount of verapamil hydrochloride ($C_{27}H_{38}N_2O_4 \cdot HCl$) dissolved at the times specified conform to *Dissolution* ⟨711⟩, *Acceptance Table 2*.

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 the *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 ($C_{27}H_{38}N_2O_4 \cdot HCl$) dissolved at the times specified conform to *Dissolution* ⟨711⟩, *Acceptance Table 2*.

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 ($C_{27}H_{38}N_2O_4 \cdot HCl$) dissolved at the times specified conform to *Dissolution* ⟨711⟩, *Acceptance Table 2*.

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 ($C_{27}H_{38}N_2O_4 \cdot HCl$) 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 ($C_{27}H_{38}N_2O_4 \cdot HCl$) dissolved at the times specified conform to *Dissolution* ⟨711⟩, *Acceptance Table 2*.

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 ($C_{27}H_{38}N_2O_4 \cdot HCl$) dissolved at the times specified conform to *Dissolution* ⟨711⟩, *Acceptance Table 2*.

Test 6: If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 6*.

Acid stage medium, Buffer stage medium, Apparatus 2, 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 ($C_{27}H_{38}N_2O_4 \cdot HCl$) 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 the sample withdrawn at time point i (mg/mL)

V = volume of *Medium*, 900 mL

L = label claim (mg/Tablet)

V_S = volume of the *Sample solution* withdrawn at each time point from the medium in the *Buffer stage* (mL)

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	5	70–90	NLT 75	NLT 80
5	8	NLT 85	NLT 85	NLT 85

The percentages of the labeled amount of verapamil hydrochloride ($C_{27}H_{38}N_2O_4 \cdot HCl$) dissolved at the times specified conform to *Dissolution ⟨711⟩*, *Acceptance Table 2*.

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

Acid stage medium: Simulated gastric fluid TS (without enzyme); 900 mL

Buffer stage medium: Simulated intestinal fluid TS (without enzyme); 900 mL

Apparatus 2: 50 rpm, with a sinker (see *Dissolution ⟨711⟩*, *Figure 2a*)

Times

Acid stage : 1 h

Buffer stage : 2, 3.5, 5, and 8 h

Diluent: 0.01 N hydrochloric acid

Dilute phosphoric acid: Dilute 5.0 mL of phosphoric acid with water to 50 mL.

Buffer: 1.74 g/L of dibasic potassium phosphate in water. Adjust to a pH of 7.5 using *Dilute phosphoric acid*.

Mobile phase: Acetonitrile and *Buffer* (650:350)

Standard solution: Prepare the corresponding USP Verapamil Hydrochloride RS solutions in *Diluent* as directed in *Table 10*. Pass through a suitable membrane filter of 0.45-µm pore size.

Table 10

Tablet Strength (mg)	Concentration of USP Verapamil Hydrochloride RS (µg/mL)
240	270
120	135
180	203

Sample solutions: Pass a portion of the solution under test at each time point through a suitable filter of 1-µm pore size, and use the filtrate.

Chromatographic system

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

Mode: LC

Detector: UV 278 nm

Column: 4.6-mm × 25-cm; 5-µm packing L7

Column temperature: 30°

Flow rate: 1.5 mL/min

Injection volume: 10 µL

Run time: NLT 1.4 times the retention time of verapamil

System suitability

Sample: *Standard solution*

Suitability requirements

Tailing factor: NMT 2.0

Relative standard deviation: NMT 2.0%

Analysis

Samples: *Standard solution* and *Sample solutions*

After 1 h in the *Acid stage medium*, withdraw 10 mL of the solution under test. Carefully transfer the dosage form including the sinker to a vessel containing the *Buffer stage medium*, previously warmed to 37 ± 0.5°.

Calculate the percentage of the labeled amount of verapamil hydrochloride ($C_{27}H_{38}N_2O_4 \cdot HCl$) dissolved in the *Acid stage medium*:

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

r_U = peak response of verapamil from the *Sample solutions*

r_S = peak response of verapamil from the *Standard solution*

C_S = concentration of USP Verapamil Hydrochloride RS in the *Standard solution* (mg/mL)

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

L = label claim (mg/Tablet)

Calculate the concentration (C_i) of verapamil hydrochloride ($C_{27}H_{38}N_2O_4 \cdot HCl$) in the sample withdrawn from the vessel at each *Buffer stage* time point (i):

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

r_U = peak response of verapamil from the *Sample solution* at each time point (i)

r_S = peak response of verapamil from the *Standard solution*

C_S = concentration of USP Verapamil Hydrochloride RS in the *Standard solution* (mg/mL)

Calculate the percentage of the labeled amount of verapamil hydrochloride ($C_{27}H_{38}N_2O_4 \cdot HCl$) 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 verapamil hydrochloride in the *Sample solution* at the specified time point i (mg/mL)

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

L = label claim (mg/Tablet)

V_S = volume of the *Sample solution* withdrawn at each time point (mL)

Tolerances: See *Table 11*.

Table 11

Time Point (*i*)	Time (h)	Amount Dissolved (%)		
		Tablet Strength—240 mg	Tablet Strength—180 mg	Tablet Strength—120 mg
1	1	7–20	7–20	10–21
2	2	15–30	15–30	18–33
3	3.5	31–60	31–60	30–55
4	5	55–85	55–85	50–82
5	8	NLT 85	NLT 85	NLT 85

The percentages of the labeled amount of verapamil hydrochloride ($C_{27}H_{38}N_2O_4 \cdot HCl$) dissolved at the times specified conform to *Dissolution* ⟨711⟩, *Acceptance Table 2*.

• **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 unspecified degradation product in the portion of Tablets taken:

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

r_U = peak response for each unspecified degradation product from the *Sample solution*

r_T = sum of all peak responses from the *Sample solution*

Acceptance criteria: See *Table 12*.

Table 12

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Verapamil related compound B[a]	0.85	—
Verapamil	1.0	—
Any unspecified degradation product	—	0.5
Total degradation products	—	1.0

[a] For resolution measurement only. Do not include it in the total.

ADDITIONAL REQUIREMENTS

• **Packaging and Storage:** Preserve in tight, light-resistant containers. Store at controlled room temperature.

• **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, 4-[(3,4-Dimethoxyphenethyl)(methyl)amino]-2-(3,4-dimethoxyphenyl)-2-isopropylbutanenitrile hydrochloride.

$C_{26}H_{36}N_2O_4 \cdot HCl$ 477.04

Auxiliary Information - Please check for your question in the FAQs before contacting USP.

Topic/Question	Contact	Expert Committee
VERAPAMIL HYDROCHLORIDE EXTENDED-RELEASE TABLETS	Documentary Standards Support	SM22020 Small Molecules 2
REFERENCE STANDARD SUPPORT	RS Technical Services RSTECH@usp.org	SM22020 Small Molecules 2

Chromatographic Database Information: Chromatographic Database

Most Recently Appeared In:
Pharmacopeial Forum: Volume No. PF 43(2)

Current DocID: GUID-42ECE4EC-BB14-49CB-A2A5-A813E0B42364_5_en-US
Previous DocID: GUID-42ECE4EC-BB14-49CB-A2A5-A813E0B42364_3_en-US
DOI: https://doi.org/10.31003/USPNF_M88099_05_01
DOI ref: cqd0p