Verapamil Hydrochloride Extended-Release Capsules

DEFINITION

Verapamil Hydrochloride Extended-Release Capsules 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*.

ASSAY

- **PROCEDURE**

Solution A: 0.01 N sodium acetate in water containing 33 mL/L of glacial acetic acid

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

System suitability solution: 0.12 mg/mL of USP Verapamil Hydrochloride RS and 0.1 mg/mL of USP Verapamil Related Compound B RS in *Mobile phase*

Standard solution: 0.12 mg/mL of USP Verapamil Hydrochloride RS in *Mobile phase*

Sample stock solution: Nominally 1.2 mg/mL of verapamil hydrochloride prepared as follows. Transfer an equivalent to 240 mg of verapamil hydrochloride, from the pool of Capsule contents (NLT 20), to a 200-mL volumetric flask. Add about 150 mL of *Mobile phase* (prewarm the *Mobile phase* to 45°). While sonicating, stir for 1 h, cool to room temperature, dilute with *Mobile phase* to volume, and mix. Centrifuge a portion for 20 min, and use the supernatant.

Sample solution: Nominally 0.12 mg/mL of verapamil hydrochloride in *Mobile phase* from the *Sample stock solution*

Chromatographic system
(See *Chromatography* ⟨621⟩, *System Suitability*.)
Mode: LC
Detector: UV 278 nm
Column: 4.6-mm × 25-cm; 5-µm packing L1
Flow rate: 1.2 mL/min
Injection volume: 20 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.* [NOTE—Verapamil related compound B elutes before verapamil.]
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 Capsules 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*.• (RB 1-Jun-2013)

Medium: 0.1 N hydrochloric acid; 900 mL
Apparatus 2: 100 rpm. •Use a• (RB 1-Jun-2013) wire helix sinker •as necessary.• (RB 1-Jun-2013)
Times: 2, 4, 8, and 24 h
Solution A and **Mobile phase:** Proceed as directed in the *Assay*.
System suitability solution: 0.25 mg/mL of USP Verapamil Hydrochloride RS and 0.2 mg/mL of USP Verapamil Related Compound B RS in *Medium*
Standard solution: 0.267 mg/mL of USP Verapamil Hydrochloride RS in *Medium*
Sample solution: Pass a portion of the solution under test through a suitable filter.
Chromatographic system
(See *Chromatography* ⟨621⟩, *System Suitability*.)
Mode: LC
Detector: UV 278 nm
Column: 4.6-mm × 25-cm; 5-µm packing L1
Flow rate: 1.2 mL/min
Injection volume: 30 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 ($C_{27}H_{38}N_2O_4 \cdot HCl$) dissolved at each time point:

$$Q_2 = (r_U/r_S) \times (C_S/L) \times V \times 100$$

$$Q_4 = (Q_2 \times V_{S1}/V) + [(r_U/r_S) \times (C_S/L) \times (V - V_{S1}) \times 100]$$

$$Q_8 = (Q_2 \times V_{S1}/V) + \{Q_4 \times V_{S2}/[V - (V_{S1} + V_{S2})]\} + \{(r_U/r_S) \times (C_S/L) \times [V - (V_{S1} + V_{S2})] \times 100\}$$

$$Q_{24} = (Q_2 \times V_{S1}/V) + \{Q_4 \times V_{S2}/[V - (V_{S1} + V_{S2})]\} + \{Q_8 \times V_{S3}/[V - (V_{S1} + V_{S2} + V_{S3})]\} + \{(r_U/r_S) \times (C_S/L) \times [V - (V_{S1} + V_{S2} + V_{S3})] \times 100\}$$

r_U = peak response of verapamil hydrochloride from the *Sample solution*
r_S = peak response of verapamil hydrochloride from the *Standard solution*
C_S = concentration of USP Verapamil Hydrochloride RS in the *Standard solution*
L = label claim (mg/Capsule)
V = initial volume of *Medium*, 900 mL
V_{Sn} = volume of *Medium* taken at each time point (mL)

Tolerances: See *Table 1*.

Table 1

Time (h)	Amount Dissolved
2	10%–25%
4	15%–40%
8	40%–65%
24	NLT 80%

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

•**Test 2:** If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 2*. **Medium, Apparatus, Times, Solution A, Mobile phase, System suitability solution, Standard solution, Sample solution, Chromatographic system, System suitability,** and **Analysis:** Proceed as directed in *Test 1*.

Tolerances: See *Table 2*.

Table 2

Time (h)	Amount Dissolved
2	NMT 25%
4	15%–40%
8	40%–65%
24	NLT 80%

• (RB 1-Jun-2013)

• **Uniformity of Dosage Units ⟨905⟩:** Meet the requirements

IMPURITIES

• **Organic Impurities**

Solution A, Mobile phase, Sample stock solution, and **System suitability:** Proceed as directed in the *Assay*.

System suitability solution: 6 µg/mL of USP Verapamil Hydrochloride RS and 4.8 µg/mL of USP Verapamil Related Compound B RS in *Mobile phase*

Standard solution: 6 µg/mL of USP Verapamil Hydrochloride RS in *Mobile phase*

Sample solution: Use the *Sample stock solution*.

Chromatographic system: Proceed as directed in the *Assay*, except for the *Injection volume* and *Run time*.

Injection volume: 50 µL

Run time: NLT 5 times the peak of verapamil

Analysis

Samples: *Standard solution* and *Sample solution*

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

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

r_U = peak response of each impurity 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

Individual impurities: NMT 0.2%

Total impurities: NMT 0.5%

ADDITIONAL REQUIREMENTS

• **Packaging and Storage:** Preserve in tight, light-resistant containers.

Add the following:

•• **Labeling:** When more than one *Dissolution* test is given, the labeling states the *Dissolution* test used only if *Test 1* is not used.• (RB 1-Jun-2013)

• **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