

Status: Currently Official on 17-Feb-2025
Official Date: Official as of 01-May-2018
Document Type: USP Monographs
DocId: GUID-EE8D5CE1-2BB4-4C69-9352-B35B9FA0837D_3_en-US
DOI: https://doi.org/10.31003/USPNF_M84411_03_01
DOI Ref: i59ra

© 2025 USPC
Do not distribute

Trandolapril and Verapamil Hydrochloride Extended-Release Tablets

DEFINITION

Trandolapril and Verapamil Hydrochloride Extended-Release Tablets contain NLT 90.0% and NMT 110.0% of the labeled amount of trandolapril ($C_{24}H_{34}N_2O_5$) and verapamil hydrochloride ($C_{27}H_{38}N_2O_4 \cdot HCl$).

IDENTIFICATION

- **A.** The retention times of the major peaks of the *Sample solution* correspond to those of the *Standard solution*, as obtained in the Assay.
- **B.** The UV absorption spectra of the trandolapril and verapamil peaks of the *Sample solution* exhibit maxima and minima at the same wavelengths as those of the corresponding peaks from the *Standard solution*, as obtained in the Assay.

ASSAY

• PROCEDURE

Buffer 1: 7 mL/L of triethylamine in water. Adjust with phosphoric acid to a pH of 3.0.

Buffer 2: 0.82 mg/mL of sodium acetate anhydrous in acetic acid

Mobile phase: Acetonitrile, methanol, and *Buffer 1* (240:160:600)

Diluent 1: Methanol and water (80:20)

Diluent 2: Acetonitrile, 2-aminoheptane, and *Buffer 2* (30:0.5:70). Adjust with 10 M sodium hydroxide to a pH of 5.0.

Standard solution: 20 µg/mL of [USP Trandolapril RS](#) and 24 µg/mL of [USP Verapamil Hydrochloride RS](#) in *Diluent 1* prepared as follows. Add *Diluent 1* to [USP Trandolapril RS](#) and [USP Verapamil Hydrochloride RS](#) to fill about 70% of the volume of the flask, sonicate to facilitate dissolution, and then dilute with *Diluent 1* to volume.

Sample solution 1: Nominally 20 µg/mL of trandolapril from NLT 5 Tablets in *Diluent 1* prepared as follows. Add *Diluent 1* to the sample, to fill about 50% of the volume of the flask, and sonicate for 45 min with occasional swirling. Cool and dilute with *Diluent 1* to volume. Pass this solution through a suitable filter of 0.45-µm pore size.

Alternatively, *Sample solution 1* can be prepared as follows. Suspend NLT 20 Tablets in 950 mL of *Diluent 2* taken in a 1-L volumetric flask.

Stir for about 2 h with a stir bar at NLT 800 rpm until the Tablets are completely disintegrated. [NOTE—Ensure that the Tablets do not adhere to the bottom of the vessel.] Remove the stir bar and rinse with *Diluent 2*. Dilute with *Diluent 2* to volume and shake thoroughly.

Centrifuge a portion of the suspension for 10 min, pipet a portion of the supernatant, and pass through a suitable filter. Discard the first 5 mL of the filtrate.

Sample solution 2: Nominally 24 µg/mL of verapamil hydrochloride in *Diluent 1* or *Diluent 2* from *Sample solution 1*

Chromatographic system

(See [Chromatography \(621\)](#), [System Suitability](#).)

Mode: LC

Detector: UV 216 nm. For *Identification B*, use a diode array detector in the range of UV 200–400 nm.

Column: 4.6-mm × 15-cm; 3-µm packing L1

Column temperature: 40°

Flow rate: 1.3 mL/min

Injection volume: 20 µL

Run time: NLT 1.5 times the retention time of the trandolapril peak

System suitability

Sample: *Standard solution*

Suitability requirements

Tailing factor: NMT 2.0 for both the trandolapril and verapamil peaks

Relative standard deviation: NMT 2.0% for both the trandolapril and verapamil peaks

Analysis

Samples: *Standard solution*, *Sample solution 1*, and *Sample solution 2*

Calculate the percentage of the labeled amount of trandolapril ($C_{24}H_{34}N_2O_5$) and 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 trandolapril from *Sample solution 1* or verapamil from *Sample solution 2*

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

C_S = concentration of [USP Trandolapril RS](#) or [USP Verapamil Hydrochloride RS](#) in the *Standard solution* ($\mu\text{g/mL}$)

C_U = nominal concentration of trandolapril in *Sample solution 1* or verapamil hydrochloride in *Sample solution 2* ($\mu\text{g/mL}$)

Acceptance criteria

Trandolapril: 90.0%–110.0%

Verapamil hydrochloride: 90.0%–110.0%

PERFORMANCE TESTS

• [DISSOLUTION \(711\)](#): TEST 1

For trandolapril

Medium: Water; 500 mL

Apparatus 2: 50 rpm

Time: 60 min

Buffer 1, Chromatographic system, and System suitability: Proceed as directed in the Assay except for the following.

Flow rate: 1 mL/min

Injection volume: 100 μL

Mobile phase: Acetonitrile and *Buffer 1* (400:600)

Standard stock solution: Prepare 0.2 mg/mL of [USP Trandolapril RS](#) as follows. Transfer [USP Trandolapril RS](#) to a suitable volumetric flask, add about 5% of the volume of the flask of acetonitrile, sonicate to dissolve, and dilute with *Medium*.

Standard solution: ($L/500$) mg/mL in *Medium* from the *Standard stock solution*, 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.

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of trandolapril ($C_{24}H_{34}N_2O_5$) dissolved:

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

r_U = peak response of trandolapril from the *Sample solution*

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

C_S = concentration of [USP Trandolapril RS](#) in the *Standard solution* (mg/mL)

V = volume of *Medium*, 500 mL

L = label claim (mg/Tablet)

Tolerances: NLT 75% (Q) of the labeled amount of trandolapril ($C_{24}H_{34}N_2O_5$) is dissolved.

For verapamil hydrochloride

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

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

Apparatus 2: 50 rpm, with a sinker (see [Dissolution \(711\)](#), [Apparatus, Figure 2a](#))

Times: 1 h in *Acid stage medium*; 2, 3.5, 5, and 8 h in *Buffer stage medium*

Mobile phase: Acetonitrile and *Buffer 1* (400:600)

Buffer 1, Chromatographic system, and System suitability: Proceed as directed in the Assay except for the following.

Detector: UV 278 nm

Flow rate: 1 mL/min

Injection volume: 10 μL

Standard stock solution: Prepare 1.34 mg/mL of [USP Verapamil Hydrochloride RS](#) as follows. Transfer [USP Verapamil Hydrochloride RS](#) to a suitable volumetric flask, add about 20% of the volume of the flask of methanol, sonicate to dissolve, cool to room temperature, and

dilute with water to volume.

Standard solution: (L/900) mg/mL in the respective *Medium* from the *Standard stock solution*, where L is the label claim in mg/Tablet

Sample solution: Withdraw 10 mL of solution at each time interval, and centrifuge at 2500 rpm for 5 min.

Analysis

Samples: *Standard solution* and *Sample solutions*

Place 1 Tablet in the sinker and place the sinker in the vessel. Prepare *Samples* as directed under *Sample solutions*.

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

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

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

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

C_S = concentration of [USP Verapamil Hydrochloride RS](#) in the *Standard solution*

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):

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

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

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

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

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

C_i = concentration of verapamil hydrochloride in the *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 in the buffer stage (mL)

Tolerances: See [Table 1](#).

Table 1

Time (h)	Amount Dissolved (%)
1	7–20
2	15–40

Time (h)	Amount Dissolved (%)
3.5	40–70
5	NLT 60
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.](#)

• **[DISSOLUTION \(711\): TEST 2](#)**

[NOTE—If the product complies with this test, the labeling indicates that the product meets USP *Dissolution Test 2*.]

For trandolapril and verapamil hydrochloride (acid stage)

[NOTE—During analysis, place the bi-layer Tablet in the dissolution vessel such that the trandolapril layer faces the bottom of the vessel.]

Medium: Simulated gastric fluid (without enzyme); 900 mL

Apparatus 2: 50 rpm, suitable wire helix sinkers

Times

Trandolapril: 45 min

Verapamil hydrochloride: 1 h

Buffer: Dissolve 6.8 g of monobasic potassium phosphate and the contents from one vial of [paired ion chromatography reagent](#) into a 1-L volumetric flask. Dissolve in approximately 950 mL of water. Adjust with dilute potassium hydroxide to a pH of 6.0 and then dilute with water to volume.

Solution A: Acetonitrile and *Buffer* (15:85)

Solution B: Acetonitrile and *Buffer* (60:40)

Mobile phase: See [Table 2](#).

Table 2

Time (min)	Solution A (%)	Solution B (%)
0	100	0
5	100	0
6	0	100
13	0	100
14	100	0
20	100	0

Standard stock solution: 0.56 mg/mL of [USP Trandolapril RS](#) in methanol

Standard solution 1: (L/900) mg/mL of [USP Trandolapril RS](#) in 0.1 N hydrochloric acid from the *Standard stock solution*, where L is the label claim in mg/Tablet. [NOTE—For better recoveries during analysis, suitable quantities of an excipient mixture used in the formulation are mixed with the *Standard solution 1* before dilution as follows: 0.85 mg of excipient mixture per milliliter of *Standard solution 1* for trandolapril/verapamil hydrochloride Tablet strength 2/180; 1.05 mg of excipient mixture per milliliter of *Standard solution 1* for trandolapril/verapamil hydrochloride Tablet strengths 1/240, 2/240, and 4/240.]

Standard solution 2: (L/900) mg/mL of [USP Verapamil Hydrochloride RS](#) in 0.1 N hydrochloric acid, 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.

Chromatographic system: Procedure for trandolapril

(See [Chromatography \(621\), System Suitability](#).)

Mode: LC

Detector: UV 210 nm