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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* (µg/mL)

C_U = nominal concentration of trandolapril in *Sample solution 1* or verapamil hydrochloride in *Sample solution 2* (µg/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):

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

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

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

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

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

C_i = concentration of verapamil hydrochloride in the *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

Column: 2-mm × 30-mm; 7-µm packing L1

Flow rate: 1 mL/min

Injection volume: 250 µL

System suitability

Sample: *Standard solution*

Suitability requirements

Tailing factor: NMT 1.5

Relative standard deviation: NMT 1.0%

Analysis

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

Use a portion of the sample withdrawn at 45 min to analyze the labeled amount of trandolapril ($C_{24}H_{34}N_2O_5$) dissolved and save the rest for analyzing verapamil hydrochloride.

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 *Standard solution 1*

C_S = concentration of USP Trandolapril RS in *Standard solution 1* (mg/mL)

V = volume of *Medium*, 900 mL

L = label claim (mg/Tablet)

Instrumental conditions: Procedure for verapamil hydrochloride

(See *Ultraviolet-Visible Spectroscopy* ⟨857⟩.)

Mode: UV

Wavelength range: 250–300 nm

Cell: 1 cm

Analysis

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

For the total labeled amount of verapamil hydrochloride ($C_{27}H_{38}N_2O_4 \cdot HCl$) dissolved in the acid stage, combine the results from the analysis of the sample withdrawn at 45 min and also at 1 h.

Calculate the percentage of the labeled amount of verapamil hydrochloride ($C_{27}H_{38}N_2O_4 \cdot HCl$) dissolved at each time point using a suitable multicomponent analysis software.

Tolerances

Trandolapril: NLT 80% (Q) of the labeled amount of trandolapril ($C_{24}H_{34}N_2O_5$) is dissolved.

Verapamil hydrochloride: See *Table 3* at 1 h.

For verapamil hydrochloride (buffer stage)

Buffer stage medium: Simulated intestinal fluid TS (without enzyme); 900 mL. Adjust with 0.2 N sodium hydroxide to a pH of 7.5.

Apparatus 2: 50 rpm

Times: 2, 3.5, 5, and 8 h

Sample solutions: Pass portions of the solution under test at each time interval through a suitable filter of 0.45-µm pore size.

Instrumental conditions and **Analysis:** Proceed as directed under verapamil hydrochloride (acid stage).

Tolerances: See *Table 3*.

Table 3

Time (h)	Amount Dissolved for Tablet Strength Trandolapril 2/ Verapamil Hydrochloride 180 (mg/mg) (%)	Amount Dissolved for All Other Tablet Strengths (%)
1	6–17	4–16
2	14–30	9–25
3.5	36–66	30–60
5	57–90	51–90

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⟩, *Content Uniformity*: Meet the requirements

IMPURITIES

• **Trandolapril Related Impurities, Procedure 1**

[Note—On the basis of the type of formulation, perform either *Trandolapril Related Impurities, Procedure 1* and *Content of Trandolapril Related Compound E*, or *Trandolapril Related Impurities, Procedure 2*. *Trandolapril Related Impurities, Procedure 2* is recommended when the formulation is a bi-layered Tablet.]

Buffer 1: Prepare a mixture of 2.72 g/L of monobasic potassium phosphate and 3.5 g/L of sodium 1-decane sulfonate. The pH of the resulting solution is about 4.68.

Buffer 2: Prepare a mixture of 2.72 g/L of monobasic potassium phosphate and 3 g/L of sodium 1-octane sulfonate. Adjust with triethylamine to a pH of 6.6.

Diluent: Acetonitrile, methanol, and water (25:25:50)

Solution A: Acetonitrile and *Buffer 1* (15:85)

Solution B: Acetonitrile, methanol, and *Buffer 2* (70:7:30)

Solution C: Acetonitrile, methanol, and *Buffer 2* (70:4:30)

Mobile phase: See *Table 4*.

Table 4

Time (min)	Solution A (%)	Solution B (%)	Solution C (%)
0	74	26	0
22	74	26	0
29	53	47	0
35	46	54	0
37	45	0	55
70	30	0	70
75	0	100	0
95	0	100	0
100	74	26	0
110	74	26	0

Trandolapril related compound A stock solution: 5 µg/mL of USP Trandolapril Related Compound A RS prepared as follows. Transfer USP Trandolapril Related Compound A RS to a suitable volumetric flask, add about 10% of the volume of the flask of methanol, and sonicate to dissolve. Cool and dilute with *Diluent* to volume.

System suitability solution: 0.125 mg/mL of USP Trandolapril RS and 0.15 µg/mL of USP Trandolapril Related Compound A RS in *Diluent* prepared as follows. Add about 30% of the volume of the flask of methanol to USP Trandolapril RS, and sonicate to dissolve. Cool, add appropriate quantities of *Trandolapril related compound A stock solution*, and dilute with *Diluent* to volume.

Standard solution: 1.2 µg/mL of USP Trandolapril RS in *Diluent*

Sample solution: Nominally 0.125 mg/mL of trandolapril in *Diluent* prepared as follows. Transfer an equivalent to 6.25 mg of trandolapril, from finely powdered Tablets (NLT 10), to a 50-mL volumetric flask, add 30 mL of *Diluent*, and sonicate for 15 min with intermittent and vigorous shaking. Cool and dilute with *Diluent* to volume. Centrifuge the resulting solution at 2500 rpm for 20 min, and pass through a suitable filter of 0.45-µm pore size.

Chromatographic system

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

Mode: LC

Detector: UV 210 nm

Column: 4.6-mm × 25-cm; 5-µm packing L1

Column temperature: 40°

Flow rate: 1 mL/min

Injection volume: 50 µL

Run times: NLT 1.5 times the retention time of trandolapril for the *Standard solution*, and NLT 7.0 times for the *System suitability solution* and the *Sample solution*

System suitability

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

Suitability requirements

Resolution: NLT 5.0 between trandolapril and trandolapril related compound A, *System suitability solution*

Tailing factor: NMT 2.0 for trandolapril, *System suitability solution*

Relative standard deviation: NMT 5.0% for trandolapril, *Standard solution*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of each impurity in the portion of Tablets 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 of trandolapril from the *Standard solution*

C_S = concentration of USP Trandolapril RS in the *Standard solution* (µg/mL)

C_U = nominal concentration of trandolapril in the *Sample solution* (µg/mL)

Acceptance criteria: See *Table 5*.

Table 5

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Trandolapril related compound E[a]	0.16	—
Trandolapril related compound A[b]	0.59	—
Trandolapril	1.00	—
Trandolapril isopropyl ester[b,c]	1.98	—

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Trandolapril related compound C[b,d]	2.15	—
Trandolapril related compound D	3.79	3.5
Any unspecified impurity	—	0.5
Total impurities[e]	—	2.0

[a] This impurity is controlled using the procedure described under *Content of Trandolapril Related Compound E*.

[b] Process related impurity and is controlled in the drug substance.

[c] (2*S*,3a*R*,7a*S*)-1-[*N*-[(*S*)-1-Carboxy-3-phenylpropyl]-L-alanyl]hexahydro-2-indolinecarboxylic acid 1-isopropyl ester.

[d] (2*S*,3a*R*,7a*S*)-1-[*N*-[(*S*)-1-Carboxy-3-cyclohexylpropyl]-L-alanyl]hexahydro-2-indolinecarboxylic acid 1-ethyl ester.

[e] Total impurities include all process related and degradation impurities from both *Trandolapril Related Impurities* and *Verapamil Hydrochloride Related Impurities* procedures except for trandolapril related compound D and do not include the content of trandolapril related compound E.

• **Trandolapril Related Impurities, Procedure 2**

[Note—*Trandolapril Related Impurities, Procedure 2* is recommended when the formulation is a bi-layered Tablet.]

Diluent: Ethanol and water (50:50)

Solution A: Acetonitrile and isopropanol (25:75)

Solution B: *Solution A*, triethylamine, phosphoric acid, and water (20:0.1:0.1:80)

Solution C: *Solution A*, triethylamine, phosphoric acid, and water (40:0.1:0.1:60)

Mobile phase: See *Table 6*.

Table 6

Time (min)	Solution B (%)	Solution C (%)
0	100	0
30	0	100
32	100	0
40	100	0

Standard stock solution: 0.05 mg/mL each of USP Trandolapril Related Compound D RS and USP Trandolapril Related Compound E RS prepared as follows. Add about 50% of the volume of the flask of alcohol and then dilute with water to volume.

System suitability solution: 0.8 mg/mL of USP Verapamil Hydrochloride RS and 4 µg/mL each of USP Trandolapril Related Compound D RS and USP Trandolapril Related Compound E RS prepared as follows. Transfer a suitable quantity of USP Verapamil Hydrochloride RS and a suitable quantity of *Standard stock solution* to a suitable volumetric flask, and dilute with *Diluent* to volume.

Standard solution: 2 µg/mL each of USP Trandolapril Related Compound D RS and USP Trandolapril Related Compound E RS from the *Standard stock solution* in *Diluent*

Sample solution: Cut off the trandolapril layer of a sufficient number of Tablets with a tablet cutter or scalpel. Finely powder the trandolapril layer mixture using a mortar and pestle and transfer a suitable quantity of the powder to a suitable volumetric flask as described in *Table 7*.

Table 7

Strength of Tablet [Trandolapril (mg)/Verapamil Hydrochloride (mg)]	Amount of Trandolapril Layer Mixture (mg)	Initial Volume of the Diluent (mL)	Volume of the Flask (mL)
1/240	1050	25	25
2/180	1050	50	50
2/240	1050	50	50
4/240	1050	100	100

Dissolve the mixture in a volume of *Diluent* per *Table 7* and stir for about 10 min. Further sonication may be necessary for complete dissolution. Remove and rinse the stir bar with *Diluent* and dilute with *Diluent* to volume. Centrifuge the contents for about 10 min and use the supernatant. Pass through a suitable filter of 0.45-µm size.

Chromatographic system

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

Mode: LC

Detector: UV 215 and 278 nm

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

Temperatures

Autosampler: 2°–8°

Column: 45°

Flow rate: 1 mL/min

Injection volume: 100 µL

Run time: NLT 3.0 times the retention time of trandolapril

System suitability

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

Suitability requirements

Resolution: NLT 2 between verapamil and trandolapril related compound E, *System suitability solution*

Relative standard deviation: NMT 2.0% for both peaks, *Standard solution*

Analysis

Samples: *Standard solution* and *Sample solution*

Overlay the chromatograms at 215 nm and at 278 nm. Disregard any peaks detected in the chromatogram at 278 nm as verapamil related impurity peaks.

Calculate the percentage of trandolapril related compound D and trandolapril related compound E impurity in the portion of Tablets 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 of trandolapril related compound D or trandolapril related compound E from the *Standard solution*

C_S = concentration of USP Trandolapril Related Compound D RS or USP Trandolapril Related Compound E RS in the *Standard solution* (µg/mL)

C_U = nominal concentration of trandolapril in the *Sample solution* (µg/mL)

Calculate the percentage of any unspecified impurity 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 unspecified impurity from the *Sample solution*

r_S = peak response of trandolapril related compound D from the *Standard solution*

C_S = concentration of USP Trandolapril Related Compound D RS in the *Standard solution* (µg/mL)

C_U = nominal concentration of trandolapril in the *Sample solution* (µg/mL)

F = relative response factor, 1.2

Acceptance criteria: See *Table 8*.

Table 8

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Trandolapril related compound E	0.66	2.0
Trandolapril	1.00	—
Trandolapril related compound D	1.97	3.5
Any unspecified impurity	—	0.5
Total impurities[a]	—	1.0

[a] Total impurities include all process related and degradation impurities from *Trandolapril Related Impurities, Procedure 2* except for trandolapril related compound D and trandolapril related compound E.

• **Content of Trandolapril Related Compound E**

[Note—The *Content of Trandolapril Related Compound E* procedure is recommended when *Trandolapril Related Impurities, Procedure 1* is used.]

Buffer: 2.72 g/L of monobasic potassium phosphate and 1.0 g/L of octane sulphonic acid. Adjust with 2% (v/v) phosphoric acid to a pH of 4.0.

Diluent 1: Acetonitrile and water (90:10)

Diluent 2: Acetonitrile and *Buffer* (20:80)

Mobile phase: See *Table 9*.

Table 9

Time (min)	Buffer (%)	Acetonitrile (%)
0	84	16
20	84	16
22	20	80
32	20	80
35	84	16
45	84	16

Standard stock solution: 0.05 mg/mL of USP Trandolapril Related Compound E RS prepared as follows. Transfer a suitable amount of USP Trandolapril Related Compound E RS to a suitable volumetric flask and add methanol to about 5% of the total volume. Sonicate to dissolve, cool, and dilute with *Diluent 2* to volume.

Standard solution: 0.5 µg/mL of USP Trandolapril Related Compound E RS in *Diluent 2* from *Standard stock solution*

Sample stock solution: Nominally 0.3 mg/mL of trandolapril prepared as follows. Transfer a quantity nominally equivalent to 7.5 mg of trandolapril, from finely powdered Tablets (NLT 10), to a 25-mL volumetric flask, add 15 mL of *Diluent 1*, and sonicate for 15 min with intermittent swirling. Cool and dilute with *Diluent 1* to volume.

Sample solution: Nominally 0.075 mg/mL of trandolapril in *Buffer* from *Sample stock solution*

Chromatographic system

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

Mode: LC

Detector: UV 210 nm

Column: 4.0-mm × 10-cm; 3-µm packing L1

Column temperature: 45°

Flow rate: 1 mL/min

Injection volume: 100 µL

Run times: NLT 1.5 times and NLT 3.5 times the retention time of trandolapril related compound E for the *Standard solution* and the *Sample solution*, respectively

System suitability

Sample: *Standard solution*

Suitability requirements

Relative standard deviation: NMT 5.0%

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of trandolapril related compound E 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 related compound E from the *Sample solution*

r_S = peak response of trandolapril related compound E from the *Standard solution*

C_S = concentration of USP Trandolapril Related Compound E RS in the *Standard solution* (µg/mL)

C_U = nominal concentration of trandolapril in the *Sample solution* (µg/mL)

Acceptance criteria: NMT 2.0%. Disregard peaks below 0.045%.

- **Verapamil Hydrochloride Related Impurities**

Buffer: 6.8 g/L of monobasic potassium phosphate and 1.0 g/L of sodium 1-octane sulfonate. Adjust with phosphoric acid to a pH of 2.5.

Diluent: Acetonitrile, methanol, and water (25:25:50)

Mobile phase: Acetonitrile and *Buffer* (33:67)

Verapamil related compound B stock solution: 0.05 mg/mL of USP Verapamil Related Compound B RS in *Diluent*

System suitability solution: 1.25 mg/mL of USP Verapamil Hydrochloride RS and 5 µg/mL of USP Verapamil Related Compound B RS in *Diluent*. Initially add *Diluent* to USP Verapamil Hydrochloride RS to fill about 50% of the volume of the flask, and sonicate to dissolve. Cool and add appropriate quantities of *Verapamil related compound B stock solution*, then dilute with *Diluent* to volume.

Standard stock solution: 0.3 mg/mL of USP Verapamil Hydrochloride RS in *Mobile phase*. Initially add *Mobile phase* to about 70% of the volume of the flask, and sonicate to dissolve. Cool, and dilute with *Mobile phase* to volume.

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

Sample solution: Nominally 1.2 mg/mL of verapamil hydrochloride in *Mobile phase* prepared as follows. Transfer a quantity equivalent to 240 mg of verapamil hydrochloride, from finely powdered Tablets (NLT 10), to a 200-mL volumetric flask, add 150 mL of *Mobile phase*, and sonicate for 30 min with intermittent vigorous shaking. Cool, and dilute with *Mobile phase* to volume. Pass through a suitable filter of 0.45-µm pore size.

Chromatographic system

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

Mode: LC

Detector: UV 278 nm

Column: 4.0-mm × 10-cm; 3-µm packing L1

Column temperature: 30°

Flow rate: 1.2 mL/min

Injection volume: 10 µL

Run times: NLT 1.6 times the retention time of verapamil for the *Standard solution*, and NLT 3.0 times for the *System suitability solution* and the *Sample solution*

System suitability

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

Suitability requirements

Resolution: NLT 1.5 between verapamil related compound B and verapamil, *System suitability solution*

Relative standard deviation: NMT 5.0%, *Standard solution*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of each impurity in the portion of Tablets 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 of the 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: Disregard peaks below 0.02%.

Any other individual unknown impurity: NMT 0.5%

Total impurities: NMT 1.0%

ADDITIONAL REQUIREMENTS

- **Packaging and Storage:** Store in a well-closed container at 15°–25°.
- **Labeling:** When more than one *Dissolution* test is given, the labeling states the test used only if *Test 1* is not used.
- **USP Reference Standards ⟨11⟩**

USP Trandolapril RS

USP Trandolapril Related Compound A RS

(2*S*,3a*R*,7a*S*)-1-[*N*-[(*S*)-1-Carboxy-3-phenylpropyl]-L-alanyl]hexahydro-2-indolinecarboxylic acid 1-methyl ester.

$C_{23}H_{32}N_2O_5$ 416.51

USP Trandolapril Related Compound D RS

(*S*)-Ethyl 2-[(3*S*,5a*S*,9a*R*,10a*S*)-3-methyl-1,4-dioxodecahydropyrazino[1,2-*a*]indol-2(1*H*)-yl)]-4-phenylbutanoate.

$C_{24}H_{32}N_2O_4$ 412.52

USP Trandolapril Related Compound E RS

(2*S*,3a*R*,7a*S*)-1-[*N*-[(*S*)-1-Carboxy-3-phenylpropyl]-L-alanyl]hexahydro-2-indolinecarboxylic acid.

$C_{22}H_{30}N_2O_5$ 402.48

USP Verapamil Hydrochloride RS

USP Verapamil Related Compound B RS

α-[2-[[2-(3,4-Dimethoxyphenyl)-ethyl]methylamino]ethyl]-3,4-dimethoxy-α-(1-methylethyl)-benzeneacetonitrile monohydrochloride.

$C_{26}H_{36}N_2O_4 \cdot HCl$ 477.05

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

Topic/Question	Contact	Expert Committee
TRANDOLAPRIL AND 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

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