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Diltiazem Hydrochloride Extended-Release Capsules

DEFINITION

Diltiazem Hydrochloride Extended-Release Capsules contain NLT 90.0% and NMT 110.0% of the labeled amount of diltiazem hydrochloride ($C_{22}H_{26}N_2O_4S \cdot HCl$).

IDENTIFICATION

- A.** The UV spectrum of the major peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the Assay.
- B.** 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: 0.79 g/L of [ammonium bicarbonate](#) in [water](#). Adjust with diluted ammonia solution or [acetic acid](#) to a pH of 8.0.

Solution B: [Acetonitrile](#)

Mobile phase: See [Table 1](#).

Table 1

Time (min)	Solution A (%)	Solution B (%)
0	95	5
2.0	95	5
5.0	60	40
13.0	60	40
16.0	30	70
20.0	30	70
20.1	95	5
25.0	95	5

Diluent: [Acetonitrile](#) and [water](#) (40:60)

Standard solution: 0.05 mg/mL of [USP Diltiazem Hydrochloride RS](#) in *Diluent*

Sample stock solution: Nominally 0.5 mg/mL of diltiazem hydrochloride from the Capsules in *Diluent* prepared as follows. Transfer a portion of finely powdered contents of NLT 20 Capsules to a suitable volumetric flask. Add *Diluent* equivalent to 80% of the flask volume, mechanically shake for 30 min, and sonicate for 60 min. Dilute with the *Diluent* to volume. Centrifuge and use the supernatant.

Sample solution: Nominally 0.05 mg/mL of diltiazem hydrochloride prepared in *Diluent* from *Sample stock solution*

Chromatographic system

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

Mode: LC

Detector: UV 240 nm. For *Identification A*, use a diode array detector in the range of 190–400 nm.

Column: 2.1-mm × 15-cm; 1.7-μm packing [L1](#)

Flow rate: 0.3 mL/min

Injection volume: 2.0 μL

System suitability

Sample: *Standard solution*

Suitability requirements

Tailing factor: NMT 2.0

Relative standard deviation: NMT 1.0%

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of diltiazem hydrochloride ($C_{22}H_{26}N_2O_4S \cdot HCl$) in the portion of Capsules taken:

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

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

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

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

C_U = nominal concentration of diltiazem hydrochloride in the *Sample solution* (mg/mL)

Acceptance criteria: 90.0%–110.0%

PERFORMANCE TESTS

• [Dissolution \(711\)](#)

For products labeled for dosing every 12 h

Test 1: If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 1*.

Medium: [Water](#); 900 mL

Apparatus 2: 100 rpm

Times: 3, 9, and 12 h

Detector: UV 237 nm

Standard solution: [USP Diltiazem Hydrochloride RS](#) in *Medium*

Sample solution: Sample per [Dissolution \(711\)](#). Dilute with *Medium* to a concentration that is similar to that of the *Standard solution*.

Tolerances: See [Table 2](#).

Table 2

Time (h)	Amount Dissolved (%)
3	10–25
9	45–85
12	NLT 70

The percentages of the labeled amount of diltiazem hydrochloride ($C_{22}H_{26}N_2O_4S \cdot HCl$) 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: [Water](#); 900 mL

Apparatus 2: 100 rpm

Times: 4, 8, 12, and 24 h

Detector: UV 237 nm

Standard solution: [USP Diltiazem Hydrochloride RS](#) in *Medium*

Sample solution: Sample per [Dissolution \(711\)](#). Dilute with *Medium* to a concentration that is similar to that of the *Standard solution*.

Tolerances: See [Table 3](#).

Table 3

Time (h)	Amount Dissolved (%)
4	10–25
8	35–60
12	55–80
24	NLT 80

The percentages of the labeled amount of diltiazem hydrochloride ($C_{22}H_{26}N_2O_4S \cdot HCl$) 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*.

Medium: 0.05 M phosphate buffer, pH 7.2; 900 mL

Apparatus 2: 50 rpm

Times: 1, 3, and 8 h

Detector: UV 237 nm

Standard solution: [USP Diltiazem Hydrochloride RS](#) in *Medium*

Sample solution: Sample per [Dissolution \(711\)](#). Dilute with *Medium* to a concentration that is similar to that of the *Standard solution*.

Tolerances: See [Table 4](#).

Table 4

Time (h)	Amount Dissolved (%)
1	NMT 15
3	45–70
8	NLT 80

The percentages of the labeled amount of diltiazem hydrochloride ($C_{22}H_{26}N_2O_4S \cdot HCl$) dissolved at the times specified conform to [Dissolution \(711\), Acceptance Table 2](#).

Test 10: If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 10*.

Buffer: Dissolve 7.1 g of [anhydrous dibasic sodium phosphate](#) in 1000 mL of [water](#), and adjust with [phosphoric acid](#) to a pH of 6.5.

Medium: *Buffer*; 900 mL

Apparatus 1: 100 rpm

Times: 1, 6, 9, and 24 h

Detector: UV 237 nm

Standard solution: [USP Diltiazem Hydrochloride RS](#) in *Medium*

Sample solution: Sample per [Dissolution \(711\)](#). Dilute with *Medium* to a concentration that is similar to that of the *Standard solution*.

Tolerances: See [Table 5](#).

Table 5

Time (h)	Amount Dissolved (%)
1	NMT 10
6	10–30
9	34–60
24	NLT 80

The percentages of the labeled amount of diltiazem hydrochloride ($C_{22}H_{26}N_2O_4S \cdot HCl$) dissolved at the times specified conform to [Dissolution \(711\), Acceptance Table 2](#).

For products labeled for dosing every 24 h

Test 2: If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 2*.

Medium: [Water](#); 900 mL

Apparatus 2: 100 rpm

Times: 1, 4, 10, and 15 h

Detector: UV 237 nm

Standard solution: [USP Diltiazem Hydrochloride RS](#) in *Medium*

Sample solution: Sample per [Dissolution \(711\)](#). Dilute with *Medium* to a concentration that is similar to that of the *Standard solution*.

Tolerances: See [Table 6](#).

Table 6

Time (h)	Amount Dissolved (%)
1	5–20

Time (h)	Amount Dissolved (%)
4	30–50
10	70–90
15	NLT 80

The percentages of the labeled amount of diltiazem hydrochloride ($C_{22}H_{26}N_2O_4S \cdot HCl$) 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*.

Medium: 0.1 N [hydrochloric acid](#); 900 mL

Apparatus 2: 100 rpm

Times: 6, 12, 18, 24, and 30 h

Detector: UV 237 nm

Standard solution: [USP Diltiazem Hydrochloride RS](#) in *Medium*

Sample solution: Sample per [Dissolution \(711\)](#). Dilute with *Medium* to a concentration that is similar to that of the *Standard solution*.

Tolerances: See [Table 7](#).

Table 7

Time (h)	Amount Dissolved (%)
6	20–45
12	25–50
18	35–70
24	NLT 70
30	NLT 85

The percentages of the labeled amount of diltiazem hydrochloride ($C_{22}H_{26}N_2O_4S \cdot HCl$) 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*.

Medium: [Water](#); 900 mL

Apparatus 1: 100 rpm

Times: 2, 4, 8, 12, and 16 h

Detector: UV 237 nm

Standard solution: [USP Diltiazem Hydrochloride RS](#) in *Medium*

Sample solution: Sample per [Dissolution \(711\)](#). Dilute with *Medium* to a concentration that is similar to that of the *Standard solution*.

Tolerances: See [Table 8](#).

Table 8

Time (h)	Amount Dissolved (%)
2	NMT 25
4	25–50
8	60–85
12	NLT 70
16	NLT 80

The percentages of the labeled amount of diltiazem hydrochloride ($C_{22}H_{26}N_2O_4S \cdot HCl$) 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*.

Buffer: Transfer 115 mL of [acetic acid](#) to a 10-L volumetric flask, dilute with [water](#) to volume, and mix (*Solution A*). Transfer 165.4 g of [anhydrous sodium acetate](#) to a 10-L volumetric flask, dilute with [water](#) to volume, and mix (*Solution B*). Mix 4410 mL of *Solution A* with 1590 mL of *Solution B*. Adjust, if necessary, with the addition of *Solution A* or *Solution B* to a pH of 4.2 ± 0.05 .

Medium: *Buffer*; 900 mL

Apparatus 2: 100 rpm

Times: 1, 4, 10, and 15 h

Detector: UV 237 nm

Standard solution: [USP Diltiazem Hydrochloride RS](#) in *Medium*

Sample solution: Sample per [Dissolution \(711\)](#). Dilute with *Medium* to a concentration that is similar to that of the *Standard solution*.

Tolerances: See [Table 9](#).

Table 9

Time (h)	Amount Dissolved (%)
1	NMT 10
4	15–35
10	65–85
15	NLT 80

The percentages of the labeled amount of diltiazem hydrochloride ($C_{22}H_{26}N_2O_4S \cdot HCl$) dissolved at the times specified conform to [Dissolution \(711\)](#), [Acceptance Table 2](#).

Test 8: If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 8*.

Medium: [Water](#); 900 mL

Apparatus 2: 100 rpm

Times: 1, 4, 10, and 15 h

Detector: UV 237 nm

Standard solution: [USP Diltiazem Hydrochloride RS](#) in *Medium*

Sample solution: Sample per [Dissolution \(711\)](#). Dilute with *Medium* to a concentration that is similar to that of the *Standard solution*.

Tolerances: See [Table 10](#).

Table 10

Time (h)	Amount Dissolved (%)
1	5–20
4	30–50
10	60–90
15	NLT 80

The percentages of the labeled amount of diltiazem hydrochloride ($C_{22}H_{26}N_2O_4S \cdot HCl$) dissolved at the times specified conform to [Dissolution \(711\)](#), [Acceptance Table 2](#).

Test 9: If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 9*.

[NOTE—Perform the test separately in each of the two media.]

Medium 1: 0.1 N [hydrochloric acid](#); 900 mL

Medium 2: Simulated intestinal fluid TS, prepared without enzyme and adjusted to a pH of 7.5 ± 0.1 ; 900 mL

Apparatus 2: 75 rpm

Time for Medium 1: 2 h

Times for Medium 2: 2, 12, 18, and 24 h

Detector: UV 237 nm

Standard solution: [USP Diltiazem Hydrochloride RS](#) in *Medium*

Sample solution: Sample per [Dissolution \(711\)](#). Dilute with *Medium* to a concentration that is similar to that of the *Standard solution*.

Table 11

Time (h)	Amount Dissolved, Medium 1 (%)	Amount Dissolved, Medium 2 (%)
2	0–5	20–45
12	–	35–55
18	–	NLT 60
24	–	NLT 80

The percentages of the labeled amount of diltiazem hydrochloride ($C_{22}H_{26}N_2O_4S \cdot HCl$) dissolved at the times specified conform to [Dissolution \(711\), Acceptance Table 2](#).

Test 11: If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 11*.

Medium: 0.1 N [hydrochloric acid](#); 900 mL

Apparatus 2: 100 rpm

Times: 1, 6, 12, and 18 h

Detector: UV 237 nm

Standard solution: [USP Diltiazem Hydrochloride RS](#) in *Medium*

Sample solution: Sample per [Dissolution \(711\)](#). Dilute with *Medium* to a concentration that is similar to that of the *Standard solution*.

Tolerances: See [Table 2](#).

Table 12

Time (h)	Amount Dissolved (%)
1	NMT 10
6	30–40
12	36–58
18	NLT 85

The percentages of the labeled amount of diltiazem hydrochloride ($C_{22}H_{26}N_2O_4S \cdot HCl$) dissolved at the times specified conform to [Dissolution \(711\), Acceptance Table 2](#).

Test 12: If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 12*. Proceed as directed in [Dissolution \(711\), Procedure, Apparatus 1 and Apparatus 2, Extended-Release Dosage Forms](#).

Medium: [Water](#); 900 mL

Apparatus 1: 100 rpm

Times: 2, 8, 14, and 24 h

Detector: UV 237 nm

Standard solution: [USP Diltiazem Hydrochloride RS](#) in *Medium*

Sample solution: Sample per [Dissolution \(711\)](#). Dilute with *Medium* to a concentration that is similar to that of the *Standard solution*.

Tolerances: See [Table 13](#).

Table 13

Time (h)	Amount Dissolved (%)
2	NMT 20
8	30–55
14	NLT 65
24	NLT 80

The percentages of the labeled amount of diltiazem hydrochloride ($C_{22}H_{26}N_2O_4S \cdot HCl$) dissolved at the times specified conform to [Dissolution \(711\), Acceptance Table 2](#).

Test 13: If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 13*. Proceed as directed in [Dissolution \(711\), Procedure, Apparatus 1 and Apparatus 2, Extended-Release Dosage Forms](#).

Medium: [Water](#); 900 mL

Apparatus 1: 100 rpm

Times: 2, 8, 14, and 24 h

Detector: UV 237 nm

Standard solution: [USP Diltiazem Hydrochloride RS](#) in *Medium*

Sample solution: Sample per [Dissolution \(711\)](#). Dilute with *Medium* to a concentration that is similar to that of the *Standard solution*.

Tolerances: See [Table 14](#).

Table 14

Time (h)	Amount Dissolved (%)
2	NMT 20
8	30–55
14	60–80
24	NLT 80

The percentages of the labeled amount of diltiazem hydrochloride ($C_{22}H_{26}N_2O_4S \cdot HCl$) dissolved at the times specified conform to [Dissolution \(711\), Acceptance Table 2](#).

Test 14: If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 14*. Proceed as directed in [Dissolution \(711\), Procedure, Apparatus 1 and Apparatus 2, Extended-Release Dosage Forms](#).

Medium: 0.1 N [hydrochloric acid](#); 900 mL

Apparatus 2: 100 rpm

Times: 6, 12, 18, 24, and 30 h

Detector: UV 237 nm

Standard solution: [USP Diltiazem Hydrochloride RS](#) in *Medium*

Sample solution: Sample per [Dissolution \(711\)](#). Dilute with *Medium* to a concentration that is similar to that of the *Standard solution*.

Tolerances: See [Table 15](#).

Table 15

Time (h)	Amount Dissolved (%)
6	20–45
12	25–50
18	35–70
24	NLT 70
30	NLT 80

The percentages of the labeled amount of diltiazem hydrochloride ($C_{22}H_{26}N_2O_4S \cdot HCl$) dissolved at the times specified conform to [Dissolution \(711\), Acceptance Table 2](#).

Test 15: If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 15*. Proceed as directed in [Dissolution \(711\), Procedure, Apparatus 1 and Apparatus 2, Extended-Release Dosage Forms](#).

Medium: 0.05 M phosphate buffer, pH 7.5; 900 mL

Apparatus 2: 75 rpm

Times: 2, 4, 8, 12, and 16 h

Detector: UV 237 nm

Standard solution: [USP Diltiazem Hydrochloride RS](#) in *Medium*

Sample solution: Sample per [Dissolution \(711\)](#). Dilute with *Medium* to a concentration that is similar to that of the *Standard solution*.

Table 16

Time (h)	Amount Dissolved (%)
2	NMT 25
4	20–40
8	60–85
12	NLT 70
16	NLT 80

The percentages of the labeled amount of diltiazem hydrochloride ($C_{22}H_{26}N_2O_4S \cdot HCl$) dissolved at the times specified conform to [Dissolution \(711\), Acceptance Table 2](#).

Test 16: If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 16*.

Medium, Apparatus 2, Times, Standard solution, and Sample solution: Proceed as directed for *Test 3*.

Detector: UV 238 nm

Tolerances: See [Table 17](#).

Table 17

Time (h)	Amount Dissolved (%)
6	20–45
12	30–55
18	40–75
24	NLT 70
30	NLT 80

The percentages of the labeled amount of diltiazem hydrochloride ($C_{22}H_{26}N_2O_4S \cdot HCl$) dissolved at the times specified conform to [Dissolution \(711\), Acceptance Table 2](#).

Test 17: If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 17*.

Medium: 0.1 N [hydrochloric acid](#); 900 mL

Apparatus 2: 100 rpm, with wire helix sinkers

Times: 6, 12, and 30 h

Detector: UV 238 nm

Standard solution: [USP Diltiazem Hydrochloride RS](#) in *Medium*

Sample solution: Dilute with *Medium*, if necessary, to a concentration that is similar to that of the *Standard solution*.

Blank: *Medium*

Tolerances: See [Table 18](#).

Table 18

Time (h)	Amount Dissolved (%)
6	20–40
12	35–55
30	NLT 80

The percentages of the labeled amount of diltiazem hydrochloride ($C_{22}H_{26}N_2O_4S \cdot HCl$) dissolved at the times specified conform to [Dissolution \(711\), Acceptance Table 2](#).

Test 18: If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 18*.

Medium: [Water](#); 900 mL

Apparatus 1: 100 rpm

Times: 2, 4, 8, and 12 h

Detector: UV 237 nm

Standard stock solution: 0.28 mg/mL of [USP Diltiazem Hydrochloride RS](#) in *Medium* prepared as follows. To a suitable amount of [USP Diltiazem Hydrochloride RS](#) in a suitable volumetric flask, add *Medium* to 50% of the volume of the flask and sonicate for 5 min to dissolve. Dilute with *Medium* to volume.

Standard solution: 0.014 mg/mL of [USP Diltiazem Hydrochloride RS](#) in *Medium* from the *Standard stock solution*

Sample solution: At the times specified, withdraw 10 mL of the solution under test. Replace the aliquots withdrawn for analysis with equal volumes of fresh portions of *Medium* maintained at 37°. Pass the solution through a PVDF filter of 0.45-µm pore size. Discard the first 2 mL of filtrate. Dilute with *Medium* to a concentration that is similar to that of the *Standard solution*.

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the concentration of diltiazem hydrochloride ($C_{22}H_{26}N_2O_4S \cdot HCl$) in the sample withdrawn from the vessel at each time point *i*:

$$\text{Result} = (A_U/A_S) \times C_S \times D$$

A_U = absorbance of diltiazem from the *Sample solution* at each time point

A_S = absorbance of diltiazem from the *Standard solution*

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

D = dilution factor for the *Sample solution*

Calculate the percentage of the labeled amount of diltiazem hydrochloride ($C_{22}H_{26}N_2O_4S \cdot HCl$) dissolved at each time point *i*:

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

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

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

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

C_i = concentration of diltiazem hydrochloride in the *Sample solution* withdrawn at the specified time point (mg/mL)

V = volume of *Medium*, 900 mL

L = label claim (mg/Capsule)

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

Tolerances: See [Table 19](#).

Table 19

Time Point (i)	Time (h)	Amount Dissolved (%)
1	2	NMT 20
2	4	33–58
3	8	68–88
4	12	NLT 80

The percentages of the labeled amount of diltiazem hydrochloride ($C_{22}H_{26}N_2O_4S \cdot HCl$) dissolved at the times specified conform to [Dissolution \(711\), Acceptance Table 2](#).

Test 19: If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 19*.

Medium: 0.1 N [hydrochloric acid](#); 900 mL

Temperature: 37.0°–37.5°

Apparatus 2: 100 rpm, with a suitable sinker

Times: 1, 4, 12, 18, and 24 h

Detector: UV 238 nm

Cell: 0.5 mm

Standard solution: 0.4 mg/mL of [USP Diltiazem Hydrochloride RS](#) in *Medium*

Sample solution: A portion of the solution under test at the time points specified

Analysis

Samples: *Standard solution* and *Sample solution*

Use an automatic dissolution system with an appropriate dissolution software.

Calculate the percentage of the labeled amount of diltiazem hydrochloride ($C_{22}H_{26}N_2O_4S \cdot HCl$) dissolved at each time point i :

$$\text{Result} = (A_U/A_S) \times (C_S/L) \times V \times 100$$

A_U = absorbance of diltiazem from the *Sample solution* at each time point

A_S = absorbance of diltiazem from the *Standard solution*

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

L = label claim (mg/Capsule)

V = volume of *Medium*, 900 mL

Tolerances: See [Table 20](#).

Table 20

Time Point (i)	Time (h)	Amount Dissolved (%)
1	1	NMT 10
2	4	15–35
3	12	30–50
4	18	50–70
5	24	NLT 85

The percentages of the labeled amount of diltiazem hydrochloride ($C_{22}H_{26}N_2O_4S \cdot HCl$) dissolved at the times specified conform to

[Dissolution \(711\)](#), [Acceptance Table 2](#).

Test 20: If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 20*.

Dissolution Test 20 is suitable for products labeled to contain 360 mg of diltiazem hydrochloride.

Medium: 0.1 N [hydrochloric acid](#); 900 mL

Apparatus 2: 100 rpm

Times: 6, 12, 18, and 24 h

Detector: UV 237 nm

Cell: 0.05 cm

Standard solution: 0.4 mg/mL of [USP Diltiazem Hydrochloride RS](#) prepared as follows. Transfer a suitable amount of [USP Diltiazem Hydrochloride RS](#) into a suitable volumetric flask, and add [methanol](#) to 5% of the total volume of the flask to dissolve. Dilute with *Medium* to volume.

Sample solution: Pass a portion of the solution under test through a suitable filter at the time points specified.

Blank: *Medium*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the concentration of diltiazem hydrochloride ($C_{22}H_{26}N_2O_4S \cdot HCl$) in the sample withdrawn from the vessel at each time point (i):

$$\text{Result} = (A_U/A_S) \times C_S$$

A_U = absorbance of diltiazem from the *Sample solution* at each time point

A_S = absorbance of diltiazem from the *Standard solution*

C_s = concentration of [USP Diltiazem Hydrochloride RS](#) in the *Standard solution* (mg/mL)

Calculate the percentage of the labeled amount of diltiazem hydrochloride ($C_{22}H_{26}N_2O_4S \cdot HCl$) dissolved at each time point (i):

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

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

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

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

C_i = concentration of diltiazem hydrochloride in the *Sample solution* withdrawn at the specified time point (mg/mL)

V = volume of *Medium*, 900 mL

L = label claim (mg/Capsule)

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

Tolerances: See [Table 21](#).

Table 21

Time Point (i)	Time (h)	Amount Dissolved (%)
1	6	30–50
2	12	35–55
3	18	50–70
4	24	NLT 85

The percentages of the labeled amount of diltiazem hydrochloride ($C_{22}H_{26}N_2O_4S \cdot HCl$) dissolved at the times specified conform to

[Dissolution \(711\), Acceptance Table 2](#).

Test 21: If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 21*.

Medium: 0.1 N [hydrochloric acid](#); 900 mL, deaerated

Apparatus 2: 100 rpm

Times: 2, 4, 14, 18, and 24 h

Standard stock solution: 1.33 mg/mL of [USP Diltiazem Hydrochloride RS](#) in *Medium*

Standard solution: ($L/900$) mg/mL of [USP Diltiazem Hydrochloride RS](#) from the *Standard stock solution* in *Medium*, where L is the label claim in mg/Capsule

Sample solution: Pass a portion of the solution under test at the time points specified through a suitable filter.

Instrumental conditions

(See [Ultraviolet-Visible Spectroscopy \(857\)](#).)

Mode: UV

Analytical wavelength: 237 nm for 120 mg, 180 mg, and 240 mg strength capsules.

260 nm for 300 mg and 360 mg strength capsules.

Cell: 1 mm for 120 mg, 180 mg, and 240 mg strength capsules.

2 mm for 300 mg and 360 mg strength capsules.

Blank: *Medium*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of diltiazem hydrochloride ($C_{22}H_{26}N_2O_4S \cdot HCl$) dissolved at each time point (i):

$$\text{Result} = (A_u/A_s) \times (C_s/L) \times V \times 100$$

A_u = absorbance of diltiazem from the *Sample solution* at each time point

A_s = absorbance of diltiazem from the *Standard solution*

C_s = concentration of [USP Diltiazem Hydrochloride RS](#) in the *Standard solution* (mg/mL)

L = label claim (mg/Capsule)

Tolerances: See [Table 22](#).

Table 22

Time Point (i)	Time (h)	Amount Dissolved (%)
1	2	NMT 20
2	4	25–45
3	14	35–55
4	18	70–90
5	24	NLT 80

The percentages of the labeled amount of diltiazem hydrochloride ($C_{22}H_{26}N_2O_4S \cdot HCl$) dissolved at the times specified conform to [Dissolution \(711\)](#), [Acceptance Table 2](#).

Test 24: If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 24*.

Medium: [Water](#); 900 mL, degassed

Apparatus 1: 100 rpm

Times: 2, 6, 16, and 24 h

Mobile phase: [Methanol](#) and [water](#) (53:47). Add 1 mL of [trifluoroacetic acid](#) to each liter of the mixture.

Standard solution: 0.3 mg/mL of [USP Diltiazem Hydrochloride RS](#) in *Medium*

Sample solution: At the specified times, withdraw 10 mL of the solution under test and pass through a suitable filter of 0.45-µm pore size, discarding the first 3 mL of filtrate.

Chromatographic system

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

Mode: LC

Detector: UV 270 nm

Column: 4.6-mm × 7.5-cm; 3.5-µm packing [L1](#)

Column temperature: 40°

Flow rate: 1.1 mL/min

Injection volume: 10 µL

Run time: NLT 3 times the retention time of diltiazem

System suitability

Sample: *Standard solution*

Suitability requirements

Tailing factor: NMT 2.0

Relative standard deviation: NMT 3.0%

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the concentration (C_i) of diltiazem hydrochloride ($C_{22}H_{26}N_2O_4S \cdot HCl$) in the sample withdrawn from the vessel at each time point (i):

$$C_i = (r_U/r_S) \times C_S$$

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

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

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

Calculate the percentage of the labeled amount of diltiazem hydrochloride ($C_{22}H_{26}N_2O_4S \cdot HCl$) dissolved at each time point (i):

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

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

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

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

C_i = concentration of diltiazem hydrochloride in the portion of sample withdrawn at the specified time point (mg/mL)

V = volume of *Medium*, 900 mL

L = label claim (mg/Capsule)

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

Tolerances: See [Table 23](#).

Table 23

Time Point (i)	Time (h)	Amount Dissolved (%)
1	2	NMT 15
2	6	25–45
3	16	55–75
4	24	NLT 80

The percentages of the labeled amount of diltiazem hydrochloride dissolved at the times specified conform to [Dissolution \(711\)](#), [Acceptance Table 2](#).

Test 25: If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 25*.

Medium: [Water](#), deaerated, if necessary; 900 mL

Apparatus 1: 100 rpm

Times: 2, 4, 8, 12 and 16 h

Standard solution: 0.01 mg/mL of [USP Diltiazem Hydrochloride RS](#) in *Medium*. Sonicate to dissolve.

Sample solution: At the times specified, withdraw 10 mL of the solution under test and replace with an equal volume of fresh *Medium*.

Centrifuge the solution and use the clear supernatant. Dilute with *Medium* to a concentration similar to that of the *Standard solution*, if necessary. [NOTE—A centrifuge speed of 2500 rpm for 10 min may be suitable.]

Instrumental conditions

(See [Ultraviolet-Visible Spectroscopy \(857\)](#).)

Mode: UV

Analytical wavelength: 237 nm

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the concentration (C_i) of diltiazem hydrochloride ($C_{22}H_{26}N_2O_4S \cdot HCl$) in the sample withdrawn from the vessel at each time point (i):

$$\text{Result}_i = (A_u/A_s) \times C_s \times D$$

A_u = absorbance of the *Sample solution*

A_s = absorbance of the *Standard solution*

C_s = concentration of [USP Diltiazem Hydrochloride RS](#) in the *Standard solution* (mg/mL)

D = dilution factor for the *Sample solution*, if necessary

Calculate the percentage of the labeled amount of diltiazem hydrochloride ($C_{22}H_{26}N_2O_4S \cdot HCl$) dissolved at each time point (i):

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

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

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

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

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

C_i = concentration of diltiazem hydrochloride in the *Sample solution* withdrawn at the specified time point i (mg/mL)

V = volume of the *Medium*, 900 mL

L = label claim (mg/Capsule)

V_s = volume of the *Sample solution* withdrawn at each time point and replaced with *Medium* (mL)

Tolerances: See [Table 24](#).

Table 24

Time Point (i)	Time (h)	Amount Dissolved (%)
1	2	NMT 25
2	4	40–60
3	8	65–90
4	12	NLT 70
5	16	NLT 80

The percentages of the labeled amount of diltiazem hydrochloride ($C_{22}H_{26}N_2O_4S \cdot HCl$) dissolved at the times specified conform to [Dissolution \(711\)](#), [Acceptance Table 2](#).

Test 26: If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 26*.

Medium: [Water](#), deaerated; 900 mL

Apparatus 1: 100 rpm

Times: 2, 8, 14 and 24 h

Standard solution: 0.01 mg/mL of [USP Diltiazem Hydrochloride RS](#) in *Medium*. Sonicate to dissolve.

Sample solution: At the times specified, withdraw 10 mL of the solution under test and replace with an equal volume of fresh *Medium*. Pass the solution through a suitable filter of 0.45- μ m pore size, discarding the first 2-3 mL of the filtrate. Dilute with *Medium* to a concentration similar to that of the *Standard solution*, if necessary.

Instrumental conditions

(See [Ultraviolet-Visible Spectroscopy \(857\)](#).)

Mode: UV

Analytical wavelength: 237 nm

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the concentration (C_i) of diltiazem hydrochloride ($C_{22}H_{26}N_2O_4S \cdot HCl$) in the sample withdrawn from the vessel at each time point (i):

$$\text{Result}_i = (A_u/A_s) \times C_s \times D$$

A_u = absorbance of the *Sample solution*

A_s = absorbance of the *Standard solution*

C_s = concentration of [USP Diltiazem Hydrochloride RS](#) in the *Standard solution* (mg/mL)

D = dilution factor for the *Sample solution*, if necessary

Calculate the percentage of the labeled amount of diltiazem hydrochloride ($C_{22}H_{26}N_2O_4S \cdot HCl$) dissolved at each time point (i):

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

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

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

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

C_i = concentration of diltiazem hydrochloride in the *Sample solution* withdrawn at the specified time point i (mg/mL)

V = volume of the *Medium*, 900 mL

L = label claim (mg/Capsule)

V_s = volume of the *Sample solution* withdrawn at each time point and replaced with *Medium* (mL)

Tolerances: See [Table 25](#).

Table 25

Time Point (i)	Time (h)	Amount Dissolved (%)
1	2	NMT 20
2	8	40–60
3	14	NLT 60
4	24	NLT 80

The percentages of the labeled amount of diltiazem hydrochloride ($C_{22}H_{26}N_2O_4S \cdot HCl$) dissolved at the times specified conform to [Dissolution \(711\)](#), [Acceptance Table 2](#).

Test 27: If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 27*.

Medium: pH 6.0 phosphate buffer prepared as follows. Transfer 250 mL of solution containing 27.22 g/L of [monobasic potassium phosphate](#) in [water](#) to a 1000-mL volumetric flask. Add 28 mL of 0.2 N [sodium hydroxide](#) solution and dilute with [water](#) to volume; 900 mL, deaerated, if necessary.

Apparatus 2: 100 rpm, with a suitable sinker

Times: 4, 8, 12, and 24 h

Standard solution: 0.1 mg/mL of [USP Diltiazem Hydrochloride RS](#) in *Medium*. Sonicate to dissolve, if necessary.

Sample solution: At the times specified, withdraw a portion of the solution under test and pass through a suitable filter of 10- μ m pore size.

Instrumental conditions

(See [Ultraviolet-Visible Spectroscopy \(857\)](#).)

Mode: UV

Analytical wavelength: 237 nm

Cell: 1 mm

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the concentration (C_i) of diltiazem hydrochloride ($C_{22}H_{26}N_2O_4S \cdot HCl$) in the sample withdrawn from the vessel at each time point (i):

$$\text{Result}_1 = (A_U/A_S) \times C_S$$

A_U = absorbance of the *Sample solution*

A_S = absorbance of the *Standard solution*

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

Calculate the percentage of the labeled amount of diltiazem hydrochloride ($C_{22}H_{26}N_2O_4S \cdot HCl$) 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 diltiazem hydrochloride in the portion of sample withdrawn at the specified time point (mg/mL)

V = volume of *Medium*, 900 mL

L = label claim (mg/Capsule)

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

Tolerances: See [Table 26](#).

Table 26

Time Point (i)	Time (h)	Amount Dissolved (%)
1	4	10–30
2	8	40–60
3	12	60–80
4	24	NLT 80

The percentages of the labeled amount of diltiazem hydrochloride ($C_{22}H_{26}N_2O_4S \cdot HCl$) dissolved at the times specified conform to [Dissolution \(711\)](#), [Acceptance Table 2](#).

Test 28: If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 28*.

Medium: [Water](#); 900 mL, deaerated, if necessary

Apparatus 2: 100 rpm

Times: 1, 4, and 10 h

Standard solution: 0.027 mg/mL of [USP Diltiazem Hydrochloride RS](#) in *Medium*. Sonicate to dissolve, if necessary.

Sample stock solution: At the times specified, withdraw a portion of the solution under test and pass through a suitable filter of 10-μm pore size.

Sample solution: Transfer 2.5 mL of the *Sample stock solution* to 25-mL volumetric flask and dilute with *Medium* to volume.

Instrumental conditions

(See [Ultraviolet-Visible Spectroscopy \(857\)](#).)

Mode: UV

Analytical wavelength: 237 nm

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the concentration (C_i) of diltiazem hydrochloride ($C_{22}H_{26}N_2O_4S \cdot HCl$) in the sample withdrawn from the vessel at each time point (i):

$$\text{Result}_i = (A_U/A_S) \times C_S \times D$$

A_U = absorbance of the *Sample solution*

A_S = absorbance of the *Standard solution*

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

D = dilution factor for the *Sample solution*, 10

Calculate the percentage of the labeled amount of diltiazem hydrochloride ($C_{22}H_{26}N_2O_4S \cdot HCl$) dissolved at each time point (i):

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

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

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

C_i = concentration of diltiazem hydrochloride in the portion of sample withdrawn at the specified time point (mg/mL)

V = volume of *Medium*, 900 mL

L = label claim (mg/Capsule)

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

Tolerances: See [Table 27](#).

Table 27

Time Point (i)	Time (h)	Amount Dissolved (for Capsules labeled to contain 120 and 180 mg of diltiazem hydrochloride) (%)	Amount Dissolved (for Capsules labeled to contain 240 mg of diltiazem hydrochloride) (%)
1	1	NMT 30	NMT 30
2	4	42–62	36–56
3	10	NLT 80	NLT 80

The percentages of the labeled amount of diltiazem hydrochloride ($C_{22}H_{26}N_2O_4S \cdot HCl$) dissolved at the times specified conform to [Dissolution \(711\)](#), [Acceptance Table 2](#).

Test 29: If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 29*.

Medium: 0.1 N [hydrochloric acid](#); 900 mL, deaerated, if necessary

Apparatus 2: 100 rpm

Times: 6, 12, 18, 24, and 30 h

Solution A: 1 mL/L of [phosphoric acid](#) in [water](#)

Mobile phase: [Acetonitrile](#) and *Solution A* (28:72)

Standard solution: 0.016 mg/mL of [USP Diltiazem Hydrochloride RS](#) in *Medium*

Sample solution: At the times specified, withdraw a portion of the solution under test and pass through a suitable filter of 0.45- μ m pore size, discarding an appropriate volume of filtrate so that a consistent result can be obtained. Dilute with *Medium* to a concentration similar to that of the *Standard solution*. Filter through a suitable filter of 0.45- μ m pore size, discarding an appropriate volume of filtrate so that a consistent result can be obtained.

Chromatographic system

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

Mode: LC

Detector: UV 237 nm

Column: 4.6-mm $\times$ 25-cm; 5- μ m packing [L11](#)

Column temperature: 40°

Flow rate: 2 mL/min

Injection volume: 40 μ L

Run time: NLT 1.2 times the retention time of diltiazem

System suitability

Sample: *Standard solution*

[NOTE—The relative retention times for desacetyl diltiazem and diltiazem are 0.56 and 1.0, respectively.]

Suitability requirements

Tailing factor: NMT 2.0 for diltiazem

Relative standard deviation: NMT 2.0% for sum of the peak responses of desacetyl diltiazem and diltiazem

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the concentration (C_i) of diltiazem hydrochloride ($C_{22}H_{26}N_2O_4S \cdot HCl$) in the sample withdrawn from the vessel at each time point (i):

$$C_i = (r_U/r_S) \times C_S \times D$$

r_U = sum of the peak responses of desacetyl diltiazem and diltiazem from the *Sample solution*

r_S = sum of the peak responses of desacetyl diltiazem and diltiazem from the *Standard solution*

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

D = dilution factor for the *Sample solution*

Calculate the percentage of the labeled amount of diltiazem hydrochloride ($C_{22}H_{26}N_2O_4S \cdot HCl$) 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 diltiazem hydrochloride in the portion of sample withdrawn at the specified time point (mg/mL)
 V = volume of *Medium*, 900 mL
 L = label claim (mg/Capsule)
 V_s = volume of the *Sample solution* withdrawn at each time point (mL)

Tolerances: See [Table 28](#).

Table 28

Time Point (i)	Time (h)	Amount Dissolved (%)
1	6	22–45
2	12	27–52
3	18	65–90
4	24	NLT 70
5	30	NLT 85

The percentages of the labeled amount of diltiazem hydrochloride dissolved at the times specified conform to [Dissolution \(711\)](#), [Acceptance Table 2](#).

- **UNIFORMITY OF DOSAGE UNITS (905):** Meet the requirements

IMPURITIES

• **ORGANIC IMPURITIES**

Solution A, Solution B, Mobile phase, Diluent, and Chromatographic system: Proceed as directed in the Assay.

Standard solution: 2.5 µg/mL each of [USP Desacetyl Diltiazem Hydrochloride RS](#) and [USP Diltiazem Hydrochloride RS](#) in *Diluent*

Sample solution: Nominally 0.5 mg/mL of diltiazem hydrochloride from the Capsules in *Diluent* prepared as follows. Transfer a portion of the finely powdered contents of NLT 20 Capsules to a suitable volumetric flask. Add *Diluent* equivalent to 80% of the flask volume, mechanically shake for 30 min, and sonicate for 60 min. Dilute with *Diluent* to volume. Centrifuge and use the supernatant.

System suitability

Sample: *Standard solution*

[NOTE—For relative retention times, see [Table 29](#).]

Suitability requirements

Resolution: NLT 2.0 between desacetyl diltiazem and diltiazem

Relative standard deviation: NMT 3.0%

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of desacetyl diltiazem hydrochloride in the portion of Capsules taken:

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

r_U = peak response of desacetyl diltiazem from the *Sample solution*

r_S = peak response of desacetyl diltiazem from the *Standard solution*

C_S = concentration of [USP Desacetyl Diltiazem Hydrochloride RS](#) in the *Standard solution* (µg/mL)

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

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

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

C_s = concentration of [USP Diltiazem Hydrochloride RS](#) in the *Standard solution* (µg/mL)

C_u = nominal concentration of diltiazem hydrochloride in the *Sample solution* (µg/mL)

Acceptance criteria: See [Table 29](#). Disregard limit: 0.05%.

[Table 29](#)

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Diltiazem related compound H ^{a,b}	0.44	—
Diltiazem related compound G ^{b,c}	0.52	—
Diltiazem related compound C ^{b,d}	0.58	—
Diltiazem related compound D ^{b,e}	0.61	—
Diltiazem related compound E ^{b,f}	0.66	—
Desacetyl diltiazem ^g	0.75	1.5
Diltiazem related compound A ^{b,h}	0.83	—
Diltiazem related compound B ^{b,i}	0.89	—
Diltiazem	1.0	—
Any individual unspecified impurity	—	0.2
Total impurities	—	2.0

- ^a (2S,3S)-5-(2-Aminoethyl)-3-hydroxy-2-(4-hydroxyphenyl)-2,3-dihydro-1,5-benzothiazepine-4(5H)-one.
- ^b These are impurities related to the drug substance. They are not to be reported for the drug product and should not be included in the total impurities.
- ^c (2S,3S)-3-Hydroxy-2-(3-methoxyphenyl)-5-(2-(methylamino)ethyl)-2,3-dihydrobenzo[b][1,4]thiazepin-4(5H)-one.
- ^d (2S,3S)-5-[2-(Dimethylamino)ethyl]-2-(4-hydroxyphenyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl acetate.
- ^e (2S,3S)-2-(4-Methoxyphenyl)-5-[2-(methylamino)ethyl]-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepine-3-yl acetate.
- ^f (2S,3S)-3-Hydroxy-2-(4-methoxyphenyl)-2,3-dihydro-1,5-benzothiazepine-4(5H)-one.
- ^g *d-cis*-3-Hydroxy-2,3-dihydro-5-[2-(dimethylamino)ethyl]-2-(*p*-methoxyphenyl)-1,5-benzothiazepin-4(5H)-one. The acceptance criteria for this impurity is based on the hydrochloride form.
- ^h (2R,3S)-5-[2-(Dimethylamino)ethyl]-2-(4-methoxyphenyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepine-3-yl acetate.
- ⁱ (2S,3S)-2-(4-Methoxyphenyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepine-3-yl acetate.

ADDITIONAL REQUIREMENTS

- **PACKAGING AND STORAGE:** Preserve in tight containers. Store at controlled room temperature.
- **LABELING:** The labeling indicates the *Dissolution* test with which the product complies.

Change to read:

- **USP REFERENCE STANDARDS (11).**
[USP Desacetyl Diltiazem Hydrochloride RS](#)
d-cis-3-Hydroxy-2,3-dihydro-5-[2-(dimethylamino)ethyl]-2-(*p*-methoxyphenyl)-1,5-benzothiazepin-4(5H)-one hydrochloride.
 $C_{20}H_{24}N_2O_3S \cdot HCl$ Δ 408.94 Δ (CN 1-Dec-2024)
[USP Diltiazem Hydrochloride RS](#)

Topic/Question	Contact	Expert Committee
DILTIAZEM HYDROCHLORIDE EXTENDED-RELEASE CAPSULES	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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