Diltiazem Hydrochloride Extended-Release Capsules

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In accordance with the Rules and Procedures of the Council of Experts, the Small Molecules 2 Expert Committee has revised the Diltiazem Hydrochloride Extended-Release Capsules monograph. The purpose for the revision is to add *Dissolution Test 24* to accommodate FDA-approved drug products with different dissolution conditions and/or tolerances than the existing dissolution test(s). The revision also necessitates a change in the table numbering in the test for *Organic Impurities*.

- *Dissolution Test 24* was validated using a Waters Symmetry C18 brand of L1 column. The typical retention time for diltiazem is about 2 min.

The Diltiazem Hydrochloride Extended-Release Capsules Revision Bulletin supersedes the currently official monograph.

Should you have any questions, please contact Behnaz Almasi, Scientific Liaison (301-692-3412 or ba@usp.org).

Revision Bulletin
Official: March 1, 2021

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-Vis 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

Change to read:

- **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
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*.

Tolerances: See *Table 11*.

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 12*.

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*.

Tolerances: See *Table 16*.

Table 16

Time (h)	Amount Dissolved (%)
2	NMT 25
4	20–40
8	60–85

Time (h)	Amount Dissolved (%)
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

Time (h)	Amount Dissolved (%)
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*):

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

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

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

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

C_i = concentration of diltiazem hydrochloride in the *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)

V = volume of *Medium*, 900 mL

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*):

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

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

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

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

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 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*.▲ (RB 1-Mar-2021)

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

IMPURITIES

Change to read:

- **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* ▲24. ▲ (RB 1-Mar-2021)]

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* ▲24. ▲ (RB 1-Mar-2021) Disregard limit: 0.05%.

Table ▲24 ▲ (RB 1-Mar-2021)

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] (2*S*,3*S*)-5-(2-Aminoethyl)-3-hydroxy-2-(4-hydroxyphenyl)-2,3-dihydro-1,5-benzothiazepine-4(5*H*)-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] (2*S*,3*S*)-3-Hydroxy-2-(3-methoxyphenyl)-5-(2-(methylamino)ethyl)-2,3-dihydrobenzo[*b*][1,4]thiazepin-4(5*H*)-one.

[d] (2*S*,3*S*)-5-[2-(Dimethylamino)ethyl]-2-(4-hydroxyphenyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl acetate.

[e] (2*S*,3*S*)-2-(4-Methoxyphenyl)-5-[2-(methylamino)ethyl]-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepine-3-yl acetate.

[f] (2*S*,3*S*)-3-Hydroxy-2-(4-methoxyphenyl)-2,3-dihydro-1,5-benzothiazepine-4(5*H*)-one.

[g] *d-cis*-3-Hydroxy-2,3-dihydro-5-[2-(dimethylamino)ethyl]-2-(*p*-methoxyphenyl)-1,5-benzothiazepin-4(5*H*)-one. The acceptance criteria for this impurity is based on the hydrochloride form.

[h] (2*R*,3*S*)-5-[2-(Dimethylamino)ethyl]-2-(4-methoxyphenyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepine-3-yl acetate.

[i] (2*S*,3*S*)-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.
- **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(5*H*)-one hydrochloride.

$C_{20}H_{24}N_2O_3S \cdot HCl$ 408.95

USP Diltiazem Hydrochloride RS

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