Diltiazem Hydrochloride Extended-Release Capsules

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Expert Committee	Chemical Medicines Monographs 2

In accordance with section 7.04 (c) of the 2015–2020 Rules and Procedures of the Council of Experts and the Pending Monograph Guideline, this is to provide notice that the Chemical Medicines Monographs 2 Expert Committee intends to revise the Diltiazem Hydrochloride Extended-Release Capsules monograph.

Based on the supporting data received from a manufacturer awaiting FDA approval, the Expert Committee proposes to add *Dissolution Test 22*.

- The analytical procedure in *Dissolution Test 22* was validated using an X-Bridge C18 brand of L1 column. The typical retention time for diltiazem is about 3 min.

The revision also necessitates a change in the table numbering in the test for *Organic Impurities*.

The proposed revision is contingent on FDA approval of a product that meets the proposed monograph specifications. The proposed revision will be published as a Revision Bulletin and an official date will be assigned to coincide as closely as possible with the FDA approval of the associated product.

See below for additional information about the proposed text.[1]

Should you have any questions, please contact Tsion Bililign, Scientific Liaison to the Chemical Medicines Monographs 2 Expert Committee (301-816-8286 or tb@usp.org).

[1] This text is not the official version of a *USP–NF* monograph and may not reflect the full and accurate contents of the currently official monograph. Please refer to the current edition of the *USP–NF* for official text.

USP provides this text to indicate changes that we anticipate will be made official once the product subject to this proposed revision under the Pending Monograph Program receives FDA approval. Once FDA approval is granted for the associated revision request, a Revision Bulletin will be posted that will include the changes indicated herein, as well as any changes indicated in the product's final approval, combined with the text of the monograph as effective on the date of approval. Any revisions made to a monograph under the Pending Monograph Program that are posted without prior publication for comment in the *Pharmacopeial Forum* must also meet the requirements outlined in the USP Guideline on Use of Accelerated Processes for Revisions to the *USP–NF*.

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
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):

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

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

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

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

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 22:** If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 22*.

Medium: 0.1 N hydrochloric acid; 900 mL

Apparatus 2: 100 rpm

Times: 1, 6, 12, and 24 h

Mobile phase: Acetonitrile and water (35:65). Add 0.5 mL of trifluoroacetic acid for every liter of the solution.

Standard stock solution: 1.7 mg/mL of USP Diltiazem Hydrochloride RS in *Medium* prepared as follows. Weigh and transfer a portion of USP Diltiazem Hydrochloride RS to an appropriate volumetric flask, add *Medium* to 30% of the volume and sonicate to dissolve. Dilute with *Medium* to volume.

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: At the specified *Times*, withdraw 10 mL of the solution under test, pass through a suitable filter of 0.45-µm pore size, and collect the filtrate by discarding the first few milliliters. Replace with 10 mL of *Medium*.

Chromatographic system

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

Mode: LC

Detector: UV 238 nm

Column: 4.6-mm × 15-cm; 5-µm packing L1

Column temperature: 40°

Flow rate: 1.5 mL/min

Injection volume: 5 µL

Run time: NLT 1.7 times the retention time of diltiazem

System suitability

Sample: *Standard solution*

[NOTE—The relative retention times of desacetyl diltiazem and diltiazem are 0.67 and 1.00, respectively.]

Suitability requirements

Tailing factor: NMT 2.0 for diltiazem

Relative standard deviation: NMT 2.0% for the sum of the peak areas 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*):

$$\text{Result}_i = (r_T/r_S) \times C_S$$

r_T = 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)

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*):

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

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

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

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

C_i = concentration of diltiazem hydrochloride in the portion of sample withdrawn at each time point (*i*) (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 (10 mL)

Tolerances: See *Table 23*.

Table 23

Time Point (*i*)	Time (h)	Amount Dissolved (%)
1	1	0–10
2	6	NMT 55
3	12	50–95
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*. ▲ (TBD)

- **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*. ▲ (TBD)]

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*.▲ (TBD) Disregard limit: 0.05%.

▲Table 24▲ (TBD)

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

Page Information:

Not Applicable

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