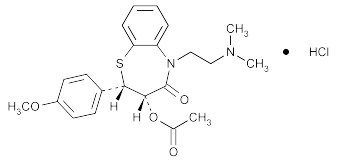
*Procedure*—Proceed as directed for *Thin-Layer Chromatography* under *Chromatography* ⟨621⟩. Examine the plate under short-wavelength UV light: any secondar y spot obtained from the *Test solution* is not more intense than the spot obtained from the *Standard solution*.

**Assay—**Dissolve about 300 mg of Diloxanide Furoate, accurately weighed, in 50.0 mL of dried pyridine, and titrate with 0.1 N tetrabutylammonium hydroxide VS, determining the endpoint potentiometrically using suitable electrodes (see *Titrimetry* ⟨541⟩). Perform a blank determination, and make any necessary correction. Each mL of 0.1 N tetrabutylammonium hydroxide is equivalent to 32.82 mg of $C_{14}H_{11}Cl_2NO_4$.

## Diltiazem Hydrochloride



$C_{22}H_{26}N_2O_4S \cdot HCl$ 450.98

1,5-Benzothiazepin-4(5*H*)-one, 3-(acetyloxy)-5-[2-(dimethylamino)ethyl]-2,3-dihydro-2-(4-methoxyphenyl)-, monohydrochloride, (+)-*cis*-.

(+)-5-[2-(Dimethylamino)ethyl]-*cis*-2,3-dihydro-3-hydroxy-2-(*p*-methoxyphenyl)-1,5-benzothiazepin-4(5*H*)-one acetate (ester) monohydrochloride [33286-22-5].

» Diltiazem Hydrochloride contains not less than 98.0 percent and not more than 102.0 per cent of $C_{22}H_{26}N_2O_4S \cdot HCl$, calculated on the dried basis.

**Packaging and storage—**Preserve in tight, light-resistant containers.

**USP Reference standards** ⟨11⟩**—**
USP Desacetyl Diltiazem Hydrochloride RS
$C_{20}H_{24}N_2O_3S \cdot HCl$ 408.95
USP Diltiazem Hydrochloride RS

**Identification—**

**A:** *Infrared Absorption* ⟨197K⟩.

**B:** The retention time of the major peak in the chromatogram of the *Assay preparation* corresponds to that in the chromatogram of the *Standard preparation,* obtained as directed in the *Assay.*

**C:** It responds to the tests for *Chloride* ⟨191⟩.

**Specific rotation** ⟨781S⟩: between +110° and +116°.

*Test solution:* 10 mg per mL, in water.

**Loss on drying** ⟨731⟩**—**Dry it at 105° for 2 hours: it loses not more than 0.5% of its weight.

**Residue on ignition** ⟨281⟩: not more than 0.1%.

**Heavy metals** ⟨231⟩: not more than 20 ppm.

**Related compounds—**

*Buffer* and *Mobile phase*—Prepare as directed in the *Assay.*

*Standard solution*—Use the *System suitability preparation* prepared as directed under *Assay.*

*Test solution*—Prepare as directed for the *Assay preparation* in the *Assay.*

*Chromatographic system*—Prepare as directed under *Assay.* The relative standard deviation of the peak response for replicate injections of the *Standard solution* is not more than 10.0%.

*Procedure*—Separately inject equal volumes (about 10 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the responses for all of the peaks. The relative retention times are about 0.65 for desacetyl diltiazem and 1.0 for diltiazem. Calculate the percentage of desacetyl diltiazem hydrochloride in the specimen of Diltiazem Hydrochloride taken by the formula:

$$10(C / W)(r_U / r_S)$$

in which $C$ is the concentration, in µg per mL, of USP Desacetyl Diltiazem Hydrochloride RS in the *Standard solution*, $W$ is the weight, in mg, of Diltiazem Hydrochloride taken, and $r_U$ and $r_S$ are the desacetyl diltiazem peak responses obtained from the *Test solution* and the *Standard solution*, respectively: not more than 0.5% of desacetyl diltiazem hydrochloride is found. Calculate the percentage of each impurity peak, other than the main peak and the desacetyl diltiazem peak, by the formula:

$$10(C / W)(r_I / r_S)$$

in which $r_I$ is the response of each impurity peak and all other quantities are as defined above: not more than 1.0% total impurities including desacetyl diltiazem hydrochloride with no individual impurity greater than 0.5% is found.

**Assay—**

*Buffer*—Dissolve 1.16 g of *d*-10-camphorsulfonic acid in 1000 mL of 0.1 M sodium acetate, adjust this solution by the addition of 0.1 N sodium hydroxide to a pH of 6.2, and mix.

*Mobile phase*—Prepare a mixture of *Buffer*, acetonitrile, and methanol (50:25:25), filter, and degas. Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

*Standard preparation*—Prepare a solution in methanol having an accurately known concentration of about 1.2 mg of USP Diltiazem Hydrochloride RS per mL.

*Assay preparation*—Transfer about 120 mg of Diltiazem Hydrochloride, accurately weighed, to a 100-mL volumetric flask, dissolve in methanol, dilute with methanol to volume, and mix.

*System suitability preparation*—Prepare a solution in methanol containing 0.012 mg each of USP Diltiazem Hydrochloride RS and USP Desacetyl Diltiazem Hydrochloride RS per mL.

*Chromatographic system*—The liquid chromatograph is equipped with a 240-nm detector and a 3.9-mm × 30-cm column that contains packing L1. The flow rate is about 1.6 mL per minute. Chromatograph the *System suitability preparation*, and record the peak responses as directed for *Procedure:* the relative retention times are about 0.65 for desacetyl diltiazem and 1.0 for diltiazem, the resolution, $R$, between desacetyl diltiazem and diltiazem is not less than 3, and the number of theoretical plates, $n$, for the diltiazem peak is not less than 1200. Chromatograph the *Standard preparation*, and record the peak responses as directed for *Procedure:* the relative standard deviation for replicate injections is not more than 2.0%.

*Procedure*—Separately inject equal volumes (about 10 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in mg, of $C_{22}H_{26}N_2O_4S \cdot HCl$ in the Diltiazem Hydrochloride taken by the formula:

$$100C(r_U / r_S)$$

in which $C$ is the concentration, in mg per mL, of USP Diltiazem Hydrochloride RS in the *Standard preparation*, and $r_U$ and $r_S$ are the peak responses obtained from the *Assay preparation* and the *Standard preparation*, respectively.

## Diltiazem Hydrochloride Extended-Release Capsules

» Diltiazem Hydrochloride Extended-Release Capsules contain not less than 90.0 per cent and not more than 110.0 per cent of the labeled amount of diltiazem hydrochloride ($C_{22}H_{26}N_2O_4S \cdot HCl$).

**Packaging and storage**—Preserve in tight containers.

**Labeling**—The labeling indicates the *Dissolution Test* with which the product complies.

**USP Reference standards** ⟨11⟩—
USP Desacetyl Diltiazem Hydrochloride RS
$C_{20}H_{24}N_2O_3S \cdot HCl$ 408.95
USP Diltiazem Hydrochloride RS

**Identification—**

**A:** Transfer 17.4 g of ammonium thiocyanate and 2.8 g of cobalt chloride to a 100-mL volumetric flask, add about 50 mL of water, and sonicate for 10 minutes. Dilute with water to volume, and mix *(Indicator solution).* Grind the contents of 1 Capsule, and transfer to a 15-mL screw-capped test tube. Add 10 mL of 0.1 N hydrochloric acid, shake, and filter. Add 2 mL of *Indicator solution* to 2 mL of the filtrate, and shake. Add 5 mL of chloroform, and shake: a blue color develops in the chloroform layer.

**B:** The retention time of the major peak in the chromatogram of the *Assay preparation* corresponds to that in the chromatogram of the *Standard preparation,* as obtained in the *Assay*.

**Dissolution** ⟨711⟩**—**

FOR PRODUCTS LABELED FOR DOSING EVERY 12 HOURS—

TEST 1—If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 1.* Proceed as directed for *Extended-Release Dosage Forms.*

*Medium:* water; 900 mL.

*Apparatus 2:* 100 rpm.

*Times:* 3, 9, and 12 hours.

*Procedure*—Determine the amount of $C_{22}H_{26}N_2O_4S \cdot HCl$ dissolved by employing UV absorption at the wavelength of maximum absorbance at about 237 nm on filtered portions of the solution under test, suitably diluted with *Medium,* if necessary, in comparison with a Standard solution having a known concentration of USP Diltiazem Hydrochloride RS in the same *Medium.*

*Tolerances*—The percentages of the labeled amount of $C_{22}H_{26}N_2O_4S \cdot HCl$ dissolved at the times specified conform to the *Acceptance Table* given.

| Time (hours) | Amount dissolved |
|---|---|
| 3 | between 10% and 25% |
| 9 | between 45% and 85% |
| 12 | not less than 70% |

**Acceptance Table**

| Level | Number Tested | Criteria |
|---|---|---|
| $L_1$ | 6 | No individual value lies outside each of the stated ranges, and no individual value is less than the stated amount at the final test time. |
| $L_2$ | 6 | The average value of the 12 units ( $L_1 + L_2$) lies within each of the stated ranges and is not less than the stated amount at the final test time. At 3 hours none of the units is outside the range of 10% to 35% of labeled content; at 9 hours none of the units is outside the range of 45% to 95% of labeled content; and at 12 hours none of the units is less than 65% of labeled content at the final test time. |
| $L_3$ | 12 | The average value of the 24 units ( $L_1 + L_2 + L_3$) lies within each of the stated ranges and is not less than the stated amount at the final test time. At 3 hours not more than 2 of the 24 units are outside the range of 10% to 35% of labeled content, and these two units must be within the range of 5% to 45% of labeled content; at 9 hours not more than 2 of the 24 units are outside the range of 45% to 95% of labeled content, and these two units must be within the range of 35% to 100% of labeled content; at 12 hours not more than 2 of the 24 units are less than 65% of labeled content at the final test time, and these two units cannot be less than 60% of labeled content at the final test time. |

TEST 4—If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 4.*

*Medium, Apparatus,* and *Procedure*—Proceed as directed under *Test 1.*

*Times:* 4, 8, 12, and 24 hours.

*Tolerances*—The percentages of the labeled amount of $C_{22}H_{26}N_2O_4S \cdot HCl$ dissolved at the times specified conform to *Acceptance Table 2*.

| Time (hours) | Amount dissolved |
|---|---|
| 4 | between 10% and 25% |
| 8 | between 35% and 60% |
| 12 | between 55% and 80% |
| 24 | not less than 80% |

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.

*Procedure*—Proceed as directed under *Test 1.*

*Times:* 1, 3, and 8 hours.

*Tolerances*—The percentages of the labeled amount of $C_{22}H_{26}N_2O_4S \cdot HCl$ dissolved at the times specified conform to *Acceptance Table 2*.

| Time (hours) | Amount dissolved |
|---|---|
| 1 | not more than 15% |
| 3 | between 45% and 70% |
| 8 | not less than 80% |

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

*Medium:* 0.05 M phosphate buffer, pH 6.5; 900 mL. Prepare the buffer employing the following method. 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.