Status: Currently Official on 17-Feb-2025
Official Date: Official as of 01-Jul-2021
Document Type: USP Monographs
DocId: GUID-A0A19A5E-EFD4-42B6-B525-53CC930D70F2_4_en-US
DOI: https://doi.org/10.31003/USPNF_M4580_04_01
DOI Ref: nb00v



# Benazepril Hydrochloride and Hydrochlorothiazide Tablets

## DEFINITION

Benazepril Hydrochloride and Hydrochlorothiazide Tablets contain NLT 90.0% and NMT 110.0% of the labeled amount of benazepril hydrochloride ($C_{24}H_{28}N_2O_5 \cdot HCl$) and hydrochlorothiazide ($C_7H_8ClN_3O_4S_2$).

## IDENTIFICATION

- **A.** The retention times of the major peaks of the *Sample solution* correspond to those of the *Standard solution*, as obtained in the *Assay*.
- **B.** The UV spectra of the major peaks of the *Sample solution* correspond to those of the *Standard solution*, as obtained in the *Assay*.

## ASSAY

- **Procedure**

**Buffer:** Dissolve 3.45 g of sodium phosphate, monobasic in 1000 mL of water. Add 2.0 mL of triethylamine. Adjust with phosphoric acid to a pH of 6.8.

**Mobile phase:** Acetonitrile and *Buffer* (32:68)

**Diluent:** Acetonitrile and water (50:50)

**Standard solution:** Concentrations of USP Benazepril Hydrochloride RS and USP Hydrochlorothiazide RS in *Diluent*, prepared as directed in *Table 1*. Sonicate to dissolve if needed.

**Table 1**

| Tablet Strength Benazepril Hydrochloride/ Hydrochlorothiazide (mg/mg) | Concentration of USP Benazepril Hydrochloride RS (mg/mL) | Concentration of USP Hydrochlorothiazide RS (mg/mL) |
|---|---|---|
| 5/6.25 | 0.10 | 0.125 |
| 10/12.5 | 0.10 | 0.125 |
| 20/25 | 0.10 | 0.125 |
| 20/12.5 | 0.10 | 0.0625 |

**Sample stock solution:** Transfer a quantity of Tablets (NLT 10) to a 200-mL volumetric flask. Add 10% of the flask volume of water and shake mechanically until the Tablets are disintegrated and well dispersed. Add another 10% of the flask volume of acetonitrile, sonicate for 20 min, then mechanically shake for an additional 20 min. Dilute with *Diluent* to volume.

**Sample solution:** Dilute the *Sample stock solution* with *Diluent* to obtain nominal concentrations of benazepril hydrochloride and hydrochlorothiazide as directed in *Table 1*. Pass a portion through a suitable filter and discard the first few milliliters of the filtrate.

**Chromatographic system**

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

**Mode:** LC

**Detector:** UV 254 nm. For *Identification B*, use a diode array detector in the range of 210–400 nm.

**Column:** 4.6-mm × 15-cm; 5-µm packing L7

**Flow rate:** 1 mL/min

**Injection volume:** 10 µL

**Run time:** NLT 1.5 times the retention time of benazepril

**System suitability**

**Sample:** *Standard solution*

[Note—The relative retention times for hydrochlorothiazide and benazepril are about 0.4 and 1.0, respectively.]

**Suitability requirements**

**Tailing factor:** NMT 2.0 for benazepril and hydrochlorothiazide

**Relative standard deviation:** NMT 2.0% for benazepril and hydrochlorothiazide

**Analysis**

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

Calculate the percentage of the labeled amount of benazepril hydrochloride ($C_{24}H_{28}N_2O_5 \cdot HCl$) in the portion of Tablets taken:

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

$r_U$ = peak response of benazepril from the *Sample solution*

$r_S$ = peak response of benazepril from the *Standard solution*

$C_S$ = concentration of USP Benazepril Hydrochloride RS in the *Standard solution* (mg/mL)

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

Calculate the percentage of the labeled amount of hydrochlorothiazide ($C_7H_8ClN_3O_4S_2$) in the portion of Tablets taken:

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

$r_U$ = peak response of hydrochlorothiazide from the *Sample solution*

$r_S$ = peak response of hydrochlorothiazide from the *Standard solution*

$C_S$ = concentration of USP Hydrochlorothiazide RS in the *Standard solution* (mg/mL)

$C_U$ = nominal concentration of hydrochlorothiazide in the *Sample solution* (mg/mL)

**Acceptance criteria:** 90.0%–110.0%

## PERFORMANCE TESTS

• **Dissolution** ⟨711⟩

**Test 1**

**Medium:** 0.1 N hydrochloric acid; 500 mL

**Apparatus 1:** 100 rpm

**Time:** 30 min

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

**Standard stock solution A:** 0.1 mg/mL of USP Benazepril Hydrochloride RS in *Medium*. Sonicate to dissolve if needed.

**Standard stock solution B:** 0.125 mg/mL of USP Hydrochlorothiazide RS in *Medium*. Sonicate to dissolve if needed.

**Standard solution:** USP Benazepril Hydrochloride RS and USP Hydrochlorothiazide RS in *Medium*, prepared as directed in *Table 2* from *Standard stock solution A* and *Standard stock solution B*

**Table 2**

| Tablet Strength Benazepril Hydrochloride/ Hydrochlorothiazide (mg/mg) | Concentration of USP Benazepril Hydrochloride RS (mg/mL) | Concentration of USP Hydrochlorothiazide RS (mg/mL) |
|---|---|---|
| 5/6.25 | 0.01 | 0.0125 |
| 10/12.5 | 0.02 | 0.025 |
| 20/12.5 | 0.04 | 0.025 |
| 20/25 | 0.04 | 0.05 |

**Sample solution:** Pass a portion of the solution under test through a suitable filter of 0.45-µm pore size. Discard the first few milliliters of the filtrate.

**Chromatographic system**

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

**Mode:** LC

**Detector:** UV 234 nm

**Column:** 4.6-mm × 15-cm; 5-µm packing L7

**Flow rate:** 0.9 mL/min

**Injection volume**

**For Tablet strength of 5/6.25 mg:** 100 µL

**For Tablet strengths of 10/12.5, 20/12.5, and 20/25 mg:** 25 µL

**Run time:** NLT 2 times the retention time of benazepril

**System suitability**

**Sample:** *Standard solution*

[NOTE—The relative retention times for hydrochlorothiazide and benazepril are about 0.5 and 1.0, respectively.]

**Suitability requirements**

**Tailing factor:** NMT 2.0 for benazepril and hydrochlorothiazide

**Relative standard deviation:** NMT 2.0% for benazepril and hydrochlorothiazide

**Analysis**

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

Calculate the percentage of the labeled amount of benazepril hydrochloride ($C_{24}H_{28}N_2O_5 \cdot HCl$) dissolved:

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

$r_U$ = peak response of benazepril from the *Sample solution*

$r_S$ = peak response of benazepril from the *Standard solution*

$C_S$ = concentration of USP Benazepril Hydrochloride RS in the *Standard solution* (mg/mL)

$L$ = label claim (mg/Tablet)

$V$ = volume of *Medium*, 500 mL

Calculate the percentage of the labeled amount of hydrochlorothiazide ($C_7H_8ClN_3O_4S_2$) dissolved:

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

$r_U$ = peak response of hydrochlorothiazide from the *Sample solution*

$r_S$ = peak response of hydrochlorothiazide from the *Standard solution*

$C_S$ = concentration of USP Hydrochlorothiazide RS in the *Standard solution* (mg/mL)

$L$ = label claim (mg/Tablet)

$V$ = volume of *Medium*, 500 mL

**Tolerances:** NLT 80% ($Q$) of the labeled amount of benazepril hydrochloride ($C_{24}H_{28}N_2O_5 \cdot HCl$) and hydrochlorothiazide ($C_7H_8ClN_3O_4S_2$) is dissolved.

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

**Medium:** 0.1 N hydrochloric acid; 500 mL

**Apparatus 1:** 100 rpm

**Time:** 30 min

**Buffer:** 3.75 g/L of potassium phosphate, dibasic in water. Adjust with phosphoric acid to a pH of 2.1.

**Mobile Phase:** Acetonitrile and *Buffer* (35:65)

**Standard stock solution:** 0.25 mg/mL of USP Hydrochlorothiazide RS, prepared as follows. Transfer a suitable amount of USP Hydrochlorothiazide RS to a volumetric flask. Add a volume of acetonitrile equivalent to 5% of the total flask volume and, if necessary, sonicate to dissolve. Dilute with *Medium* to volume.

**Standard solution:** ($L_2$/500) mg/mL of USP Hydrochlorothiazide RS from *Standard stock solution* and ($L_1$/500) mg/mL of USP Benazepril Hydrochloride RS diluted in *Medium*, where $L_1$ is the label claim for benazepril hydrochloride in mg/Tablet and $L_2$ is the label claim for hydrochlorothiazide in mg/Tablet

**Sample solution:** Pass a portion of the solution under test through a suitable filter of 0.45-µm pore size. Discard the first few milliliters of the filtrate. [NOTE—It is recommended to avoid using stainless steel cannula when sampling.]

**Chromatographic system**

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

**Mode:** LC

**Detector:** UV 240 nm for benazepril and UV 275 nm for hydrochlorothiazide

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

**Flow rate:** 1 mL/min

**Injection volume:** 20 µL

**Run time:** NLT 1.5 times the retention time of benazepril

**System suitability**

**Sample:** *Standard solution*

**Suitability requirements**

**Tailing factor:** NMT 2.0 for benazepril at 240 nm and hydrochlorothiazide at 275 nm

**Relative standard deviation:** NMT 2.0% for benazepril at 240 nm and hydrochlorothiazide at 275 nm

**Analysis**

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

Calculate the percentage of the labeled amount of benazepril hydrochloride ($C_{24}H_{28}N_2O_5 \cdot HCl$) dissolved:

$$\text{Result} = (r_U/r_S) \times (C_S/L_1) \times V \times 100$$

$r_U$ = peak response of benazepril from the *Sample solution*

$r_S$ = peak response of benazepril from the *Standard solution*

$C_S$ = concentration of USP Benazepril Hydrochloride RS in the *Standard solution* (mg/mL)

$L_1$ = label claim of benazepril hydrochloride (mg/Tablet)

$V$ = volume of *Medium*, 500 mL

Calculate the percentage of the labeled amount of hydrochlorothiazide ($C_7H_8ClN_3O_4S_2$) dissolved:

$$\text{Result} = (r_U/r_S) \times (C_S/L_2) \times V \times 100$$

$r_U$ = peak response of hydrochlorothiazide from the *Sample solution*

$r_S$ = peak response of hydrochlorothiazide from the *Standard solution*

$C_S$ = concentration of USP Hydrochlorothiazide RS in the *Standard solution* (mg/mL)

$L_2$ = label claim of hydrochlorothiazide (mg/Tablet)

$V$ = volume of *Medium*, 500 mL

**Tolerances:** NLT 80% ($Q$) of the labeled amount of benazepril hydrochloride ($C_{24}H_{28}N_2O_5 \cdot HCl$) and NLT 75% ($Q$) of the labeled amount of hydrochlorothiazide ($C_7H_8ClN_3O_4S_2$) is dissolved.

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

## IMPURITIES

- **Organic Impurities**

**Solution A:** Dissolve 3.45 g of sodium phosphate, monobasic in 1000 mL of water. Add 1.0 mL of triethylamine. Adjust with 5 N sodium hydroxide to a pH of 6.7.

**Solution B:** Acetonitrile and methanol (80:20)

**Mobile phase:** See *Table 3*.

**Table 3**

| Time (min) | Solution A (%) | Solution B (%) |
|---|---|---|
| 0 | 95 | 5 |
| 10 | 90 | 10 |
| 20 | 75 | 25 |
| 25 | 65 | 35 |
| 30 | 65 | 35 |
| 40 | 55 | 45 |
| 45 | 30 | 70 |
| 65 | 30 | 70 |
| 70 | 95 | 5 |
| 80 | 95 | 5 |

**Diluent A:** Acetonitrile and water (32:68)

**Diluent B:** Acetonitrile and water (50:50)

**Diluent C:** Acetonitrile and water (13:87)

**System suitability stock solution A:** 0.1 mg/mL each of USP Benazepril Related Compound B RS and USP Chlorothiazide RS, and 0.125 mg/mL of USP Benzothiadiazine Related Compound A RS in *Diluent A*. Sonicate to dissolve if needed.

**System suitability stock solution B:** 0.15 mg/mL of USP Benazepril Related Compound C RS prepared as follows. Transfer 3.75 mg of USP Benazepril Related Compound C RS into a 25-mL volumetric flask. Add 20 mL of *Diluent B*, sonicate, and dilute with water to volume.

**System suitability solution:** 10 µg/mL each of USP Benazepril Related Compound B RS and USP Chlorothiazide RS, 12.5 µg/mL of USP Benzothiadiazine Related Compound A RS, and 30 µg/mL of USP Benazepril Related Compound C RS from *System suitability stock solution A* and *System suitability stock solution B*, diluted with water

**Standard stock solution 1:** 0.1 mg/mL of USP Benazepril Hydrochloride RS and 0.125 mg/mL of USP Hydrochlorothiazide RS in *Diluent A* for Tablet strengths containing 5/6.25, 10/12.5, and 20/25 mg of benazepril hydrochloride and hydrochlorothiazide. Sonicate to dissolve if needed.

**Standard stock solution 2:** 0.1 mg/mL of USP Benazepril Hydrochloride RS and 0.0625 mg/mL of USP Hydrochlorothiazide RS in *Diluent A* for Tablet strength containing 20/12.5 mg of benazepril hydrochloride and hydrochlorothiazide. Sonicate to dissolve if needed.

**Standard stock solution 3:** 10 µg/mL of USP Benazepril Hydrochloride RS and 12.5 µg/mL of USP Hydrochlorothiazide RS for 5/6.25, 10/12.5, and 20/25 Tablet strengths prepared as follows. Transfer a suitable volume of *Standard stock solution 1* to an appropriate volumetric flask. Add 30% of the flask volume of *Diluent A*. Dilute with water to volume.

**Standard stock solution 4:** 10 µg/mL of USP Benazepril Hydrochloride RS and 6.25 µg/mL of USP Hydrochlorothiazide RS for 20/12.5 Tablet strength prepared as follows. Transfer a suitable volume of *Standard stock solution 2* into an appropriate volumetric flask. Add 30% of the flask volume of *Diluent A*. Dilute with water to volume.

**Standard solution:** USP Benazepril Hydrochloride RS and USP Hydrochlorothiazide RS prepared as directed in *Table 4* from *Standard stock solution 3* or *Standard stock solution 4*, diluted with *Diluent C*

**Table 4**

| Tablet Strength Benazepril Hydrochloride/ Hydrochlorothiazide (mg/mg) | Concentration of USP Benazepril Hydrochloride RS (µg/mL) | Concentration of USP Hydrochlorothiazide RS (µg/mL) |
|---|---|---|
| 5/6.25 | 2 | 2.5 |
| 10/12.5 | 2 | 2.5 |
| 20/25 | 2 | 2.5 |
| 20/12.5 | 2 | 1.25 |

**Sensitivity solution:** 0.5 µg/mL of USP Benazepril Hydrochloride RS and 0.625 µg/mL of USP Hydrochlorothiazide RS from *Standard solution*, diluted with *Diluent C*

**Sample solution:** Finely powder a quantity of Tablets (NLT 20) and transfer a portion of the powder, equivalent to 50 mg of benazepril hydrochloride, to a 50-mL volumetric flask. Add 40% of the flask volume of *Diluent A* and sonicate for 20 min with frequent shaking. Dilute with water to volume to obtain the nominal concentrations of benazepril hydrochloride and hydrochlorothiazide as given in *Table 5*.

**Table 5**

| Tablet Strength Benazepril Hydrochloride/ Hydrochlorothiazide (mg/mg) | Nominal Concentration of Benazepril Hydrochloride (mg/mL) | Nominal Concentration of Hydrochlorothiazide (mg/mL) |
|---|---|---|
| 5/6.25 | 1.0 | 1.25 |
| 10/12.5 | 1.0 | 1.25 |
| 20/25 | 1.0 | 1.25 |
| 20/12.5 | 1.0 | 0.625 |

**Chromatographic system**

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

**Mode:** LC

**Detector:** UV 254 nm

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

**Temperatures**

**Autosampler:** 5°

**Column:** 30°

**Flow rate:** 1.2 mL/min

**Injection volume:** 50 µL

**System suitability**

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

[NOTE—See *Table 6* for the relative retention times.]

**Suitability requirements**

**Resolution:** NLT 1.5 between benzothiadiazine related compound A and chlorothiazide, *System suitability solution*

**Tailing factor:** NMT 2.0 for benazepril and hydrochlorothiazide, *Standard solution*

**Relative standard deviation:** NMT 5% for benazepril and hydrochlorothiazide, *Standard solution*

**Signal-to-noise ratio:** NLT 10 for benazepril and hydrochlorothiazide, *Sensitivity solution*

**Analysis**

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

Calculate the percentage of benazepril related compound B, benazepril related compound C, or any unspecified degradation product in the portion of Tablets taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times (1/F) \times 100$$

$r_U$ = peak response of benazepril related compound B, benazepril related compound C, or any unspecified degradation product from the *Sample solution*

$r_S$ = peak response of benazepril from the *Standard solution*

$C_S$ = concentration of USP Benazepril Hydrochloride RS in the *Standard solution* (mg/mL)

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

$F$ = relative response factor (see *Table 6*)

Calculate the percentage of benzothiadiazine related compound A in the portion of Tablets taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times (1/F) \times 100$$

$r_U$ = peak response of benzothiadiazine related compound A from the *Sample solution*

$r_S$ = peak response of hydrochlorothiazide from the *Standard solution*

$C_S$ = concentration of USP Hydrochlorothiazide RS in the *Standard solution* (mg/mL)

$C_U$ = nominal concentration of hydrochlorothiazide in the *Sample solution* (mg/mL)

$F$ = relative response factor (see *Table 6*)

**Acceptance criteria:** See *Table 6*.

**Table 6**

| Name | Relative Retention Time | Relative Response Factor | Acceptance Criteria, NMT (%) |
|---|---|---|---|
| Benzothiadiazine related compound A | 0.30 | 1.85 | 1.0 |
| Chlorothiazide[a] | 0.33 | — | — |
| Hydrochlorothiazide | 0.42 | — | — |
| Benazepril related compound C | 0.61 | 0.89 | 3.0 |
| Hydrochlorothiazide dimer[a,b] | 0.76 | — | — |
| Benazepril | 1.00 | — | — |

| Name | Relative Retention Time | Relative Response Factor | Acceptance Criteria, NMT (%) |
|---|---|---|---|
| Benazepril related compound B | 1.16 | 0.95 | 0.5 |
| Benazepril related compound G[a,c] | 1.50 | — | — |
| Any unspecified degradation product | — | 1.0 | 0.2 |
| Total degradation products[d] | — | — | 2.0 |

[a] Process impurity included in the table for identification only. Process impurities are not to be reported or included in the total degradation products for the drug product.

[b] 6-Chloro-*N*-[(6-chloro-7-sulfamoyl-2,3-dihydro-4*H*-1,2,4-benzothiadiazine-4-yl 1,1-dioxide)methyl]3,4-dihydro-2*H*-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide.

[c] Ethyl (*S*)-2-{[(*S*)-1-(2-ethoxy-2-oxoethyl)-2-oxo-2,3,4,5-tetrahydro-1*H*-benzo[*b*]azepin-3-yl]amino}-4-phenylbutanoate.

[d] Excluding benzothiadiazine related compound A and benazepril related compound C.

**ADDITIONAL REQUIREMENTS**

• **Packaging and Storage:** Protect from moisture and light. Store at controlled room temperature.

• **Labeling:** When more than one *Dissolution* test is given, the labeling states the test used only if *Test 1* is not used.

***Change to read:***

• **USP Reference Standards** ⟨11⟩

USP Benazepril Hydrochloride RS

USP Benazepril Related Compound B RS

▲2-[(*S*)-3-{[(*R*)-1-Ethoxy-1-oxo-4-phenylbutan-2-yl]amino}-2-oxo-2,3,4,5-tetrahydro-1*H*-benzo[*b*]azepin-1-yl]acetic acid hydrochloride;
Also known as▲ (ERR 1-Jul-2021) (3*S*) 3-[[(1*R*)-1-(Ethoxycarbonyl)-3-phenylpropyl]amino]-2,3,4,5-tetrahydro-2-oxo-1*H*-1-benzazepine-1-acetic acid, monohydrochloride.

$C_{24}H_{28}N_2O_5 \cdot HCl$ 460.95

USP Benazepril Related Compound C RS

(3*S*)-3-[[(1*S*)-1-Carboxy-3-phenylpropyl]amino-2,3,4,5-tetrahydro-2-oxo-1*H*-1-benazepine]-1-acetic acid;
Also known as (*S*)-2-{[(*S*)-1-(Carboxymethyl)-2-oxo-2,3,4,5-tetrahydro-1*H*-benzo[*b*]azepin-3-yl]amino}-4-phenylbutanoic acid.

$C_{22}H_{24}N_2O_5$ 396.44

USP Benzothiadiazine Related Compound A RS

4-Amino-6-chloro-1,3-benzenedisulfonamide.

$C_6H_8ClN_3O_4S_2$ 285.73

USP Chlorothiazide RS

USP Hydrochlorothiazide RS



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

| Topic/Question | Contact | Expert Committee |
|---|---|---|
| BENAZEPRIL HYDROCHLORIDE AND HYDROCHLOROTHIAZIDE TABLETS | Documentary Standards Support | SM22020 Small Molecules 2 |
| REFERENCE STANDARD SUPPORT | RS Technical Services RSTECH@usp.org | SM22020 Small Molecules 2 |

**Chromatographic Database Information:** Chromatographic Database

**Most Recently Appeared In:**
Pharmacopeial Forum: Volume No. 45(3)

**Current DocID: GUID-A0A19A5E-EFD4-42B6-B525-53CC930D70F2_4_en-US**

**DOI: https://doi.org/10.31003/USPNF_M4580_04_01**

**DOI ref: nb00v**