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Quinapril and Hydrochlorothiazide Tablets

DEFINITION

Quinapril and Hydrochlorothiazide Tablets contain NLT 95.0% and NMT 105.0% of the labeled amounts of quinapril ($C_{25}H_{30}N_2O_5$) and hydrochlorothiazide ($C_7H_8ClN_3O_4S_2$).

IDENTIFICATION

• **A.** The relative retention times of the major peaks of the *Sample solution* correspond to those of the *Standard solution*, as obtained in the *Assay*.

Add the following:

▲• **B.** The UV spectra of the major peaks of the *Sample solution* correspond to those of the *Standard solution*, as obtained in the *Assay*.▲ (USP 1-May-2023)

ASSAY

Change to read:

• **Procedure**

Solution A: Dissolve 1.36 g▲▲ (USP 1-May-2023) of monobasic potassium phosphate in ▲1000 mL of▲ (USP 1-May-2023) water, add 2 mL of triethylamine, and adjust with phosphoric acid to a pH of 3.0. Pass through a suitable ▲▲ (USP 1-May-2023) filter of 0.45-µm pore size.

Solution B: Acetonitrile

Mobile phase: See *Table 1*.

Table 1

Time (min)	Solution A (%)	Solution B (%)
0	75	25
8	40	60
12	40	60
13	75	25
18	75	25

Diluent: *Solution A* and *Solution B* (50:50)

Standard stock solution A: 0.45 mg/mL of USP Quinapril Hydrochloride RS in *Diluent*

Standard stock solution B: 0.5 mg/mL of USP Hydrochlorothiazide RS in *Diluent*

Standard solution: ▲Known concentrations of USP Quinapril Hydrochloride RS and USP Hydrochlorothiazide RS in *Diluent* from▲ (USP 1-May-2023) *Standard stock solution A* and *Standard stock solution B* ▲▲ (USP 1-May-2023) as given in *Table 2*.

Table 2

▲

Tablet Strength Quinapril/Hydrochlorothiazide (mg/mg)	USP Quinapril Hydrochloride RS (mg/mL)	USP Hydrochlorothiazide RS (mg/mL)
10/12.5	0.0225	0.025
20/12.5	0.0225	0.0125
20/25	0.0225	0.025

▲ (USP 1-May-2023)

Sample stock solution: Transfer 5 Tablets into a 250-mL volumetric flask, add 50 mL of *Diluent*, and sonicate for 15 min. Add about 50 mL of acetonitrile, and sonicate for 15 min with shaking. Add 50 mL of *Diluent*, and sonicate for 15 min. Dilute with *Diluent* to volume. ▲Pass through a suitable filter of 0.45-µm pore size.▲ (USP 1-May-2023)

Sample solution: ▲Nominally▲ (USP 1-May-2023) 0.02 mg/mL of quinapril in *Diluent* from the *Sample stock solution*. [NOTE—The hydrochlorothiazide concentration may vary depending on the ratio of quinapril ▲▲ (USP 1-May-2023) to hydrochlorothiazide in the Tablet.]

Chromatographic system

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

Mode: LC

Detector: UV 215 nm. ▲For *Identification B*, use a diode array detector in the range of 190–400 nm.▲ (USP 1-May-2023)

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

Column temperature: 35°

Flow rate: 1 mL/min

Injection volume: 20 µL

System suitability

Sample: *Standard solution*

Suitability requirements

▲▲ (USP 1-May-2023)

Tailing factor: NMT 2.0 for quinapril and hydrochlorothiazide

Relative standard deviation: NMT 2.0% for quinapril and hydrochlorothiazide

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of ▲the labeled amount of▲ (USP 1-May-2023) quinapril ($C_{25}H_{30}N_2O_5$) in the portion of Tablets taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times (M_{r1}/M_{r2}) \times 100$$

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

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

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

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

M_{r1} = molecular weight of quinapril, 438.52

M_{r2} = molecular weight of quinapril hydrochloride, 474.98

Calculate the percentage of ▲the labeled amount of▲ (USP 1-May-2023) 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: 95.0%–105.0% ▲for both quinapril and hydrochlorothiazide▲ (USP 1-May-2023)

PERFORMANCE TESTS

Change to read:

• **Dissolution** ⟨711⟩

Medium: Water; 900 mL

Apparatus 1: 100 rpm

Time: 20 min

Solution A, ▲**Solution B,**▲ (USP 1-May-2023) **Mobile phase,** ▲**Diluent, Standard stock solution A, Standard stock solution B, Standard solution,**▲ (USP 1-May-2023) **Chromatographic system,** and **System suitability:** Proceed as directed in the *Assay*.

▲▲ (USP 1-May-2023)

Sample solution: Pass a portion of the solution under test through a suitable ▲▲ (USP 1-May-2023) filter of 0.45-µm pore size, discarding the first few milliliters.

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of ▲the labeled amount of▲ (USP 1-May-2023) quinapril ($C_{25}H_{30}N_2O_5$) dissolved:

$$\text{Result} = (r_U/r_S) \times (C_S/L) \times V \times (M_{r1}/M_{r2}) \times 100$$

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

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

C_S = concentration of USP Quinapril Hydrochloride RS in the *Standard solution*▲(mg/mL)▲ (USP 1-May-2023)

L = label claim for quinapril ▲▲ (USP 1-May-2023) (mg/Tablet)

V = volume of *Medium*, 900 mL

M_{r1} = molecular weight of quinapril, 438.52

M_{r2} = molecular weight of quinapril hydrochloride, 474.98

Calculate the percentage of ▲the labeled amount of▲ (USP 1-May-2023) 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)▲ (USP 1-May-2023)

L = label claim for hydrochlorothiazide (mg/Tablet)

V = volume of *Medium*, 900 mL

Tolerances: NLT 80% (Q) of the labeled amounts of quinapril ▲($C_{25}H_{30}N_2O_5$)▲ (USP 1-May-2023) and hydrochlorothiazide ($C_7H_8ClN_3O_4S_2$) is dissolved.

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

IMPURITIES

Change to read:

• **Organic Impurities**

Solution A, ▲**Solution B,**▲ (USP 1-May-2023) **Diluent,** and ▲**Sample stock solution:**▲ (USP 1-May-2023) Prepare as directed in the *Assay*.

Mobile phase: See *Table 3*.

Table 3

Time (min)	Solution A (%)	Solution B (%)
0	90	10
10	60	40
30	30	70
31	90	10
40	90	10

▲**Sensitivity solution:** 0.22 µg/mL of USP Quinapril Hydrochloride RS in *Diluent*▲ (USP 1-May-2023)

Standard solution: 0.45 µg/mL each of ▲USP Quinapril Hydrochloride RS, USP Quinapril Related Compound A RS, and USP Quinapril Related Compound B RS,▲ (USP 1-May-2023) and 0.5 µg/mL each of ▲USP Hydrochlorothiazide RS and USP Benzothiadiazine Related Compound A RS▲ (USP 1-May-2023) in *Diluent*

▲▲ (USP 1-May-2023)

Sample solution: For Tablet strengths of 10 mg/12.5 mg and 20 mg/12.5 mg of quinapril▲▲ (USP 1-May-2023) /hydrochlorothiazide, use the *Sample stock solution* as is. For a Tablet strength of 20 mg/25 mg of quinapril▲▲ (USP 1-May-2023) /hydrochlorothiazide, dilute 5 mL of the *Sample stock solution* with *Diluent* to 10 mL.

Chromatographic system

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

Mode: LC

Detector: UV 215 nm

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

Temperatures

Autosampler: 5°

Column: 35°

Flow rate: 1 mL/min

Injection volume: 20 µL

System suitability

Samples: ▲*Sensitivity solution* and▲ (USP 1-May-2023) *Standard solution*

Suitability requirements

▲▲ (USP 1-May-2023)

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

Relative standard deviation: NMT 5.0% for quinapril and hydrochlorothiazide, *Standard solution*

▲**Signal-to-noise ratio:** NLT 10, *Sensitivity solution*▲ (USP 1-May-2023)

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of quinapril related compound A and quinapril related compound B in the portion of Tablets taken:

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

r_U = peak response of quinapril related compound A or quinapril related compound B from the *Sample solution*

r_S = peak response of ▲quinapril related compound A or quinapril related compound B▲ (USP 1-May-2023) from the *Standard solution*

C_S = concentration of USP Quinapril Related Compound A RS ▲or▲ (USP 1-May-2023) USP Quinapril Related Compound B RS in the *Standard solution* (mg/mL)

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

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

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

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

r_S = peak response of benzothiadiazine related compound A from the *Standard solution*

C_S = concentration of USP Benzothiadiazine Related Compound A RS in the *Standard solution* (mg/mL)

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

Calculate the percentage of any ▲unspecified▲ (USP 1-May-2023) impurity in the portion of Tablets taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times (M_{r1}/M_{r2}) \times 100$$

r_U = peak response of ▲any unspecified▲ (USP 1-May-2023) impurity from the *Sample solution*

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

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

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

M_{r1} = molecular weight of quinapril, 438.52

M_{r2} = molecular weight of quinapril hydrochloride, 474.98

Acceptance criteria: See *Table 4*. ▲The reporting threshold is 0.1%.▲ (USP 1-May-2023)

Table 4

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Benzothiadiazine related compound A▲▲ (USP 1-May-2023)	0.42	1.0
Chlorothiazide▲[a],▲ (USP 1-May-2023) [b]	0.45	—
Hydrochlorothiazide▲▲ (USP 1-May-2023)	0.49	—
5-Chlorohydrochlorothiazide[b]▲,[c]▲ (USP 1-May-2023)	0.65	—
Quinapril related compound B▲▲ (USP 1-May-2023)	0.74	3.0
Hydrochlorothiazide dimer[b]▲,[d]▲ (USP 1-May-2023)	0.78	—

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Quinapril methyl ester[b▲,e▲] (USP 1-May-2023)	0.91	—
Quinapril▲▲ (USP 1-May-2023)	1.00	—
Quinapril isopropyl ester[b▲,f▲] (USP 1-May-2023)	1.10	—
Hexahydroquinapril[b▲,g▲] (USP 1-May-2023)	1.23	—
Quinapril related compound A▲▲ (USP 1-May-2023)	1.59	1.0
Quinapril, benzyl ester[b▲,h▲] (USP 1-May-2023)	1.94	—
Any ▲▲ (USP 1-May-2023) unspecified impurity	—	0.2
Total impurities[i]	—	2.0

[a] ▲6-Chloro-2*H*-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide.▲ (USP 1-May-2023)

[b] Process related impurity, monitored in the drug substance.

[c] ▲5,6-Dichloro-3,4-dihydro-2*H*-benzothiadiazine-7-sulfonamide 1,1-dioxide.▲ (USP 1-May-2023)

[d] ▲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.

[e] (*S*)-2-{[(*S*)-1-Methoxy-1-oxo-4-phenylbutan-2-yl]-L-alanyl}-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid.

[f] (*S*)-2-{[(*S*)-1-Isopropoxy-1-oxo-4-phenylbutan-2-yl]-L-alanyl}-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid.

[g] (*S*)-2-{[(*S*)-4-Cyclohexyl-1-ethoxy-1-oxobutan-2-yl]-L-alanyl}-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid.

[h] Benzyl (*S*)-2-{[(*S*)-1-ethoxy-1-oxo-4-phenylbutan-2-yl]-L-alanyl}-1,2,3,4-tetrahydroisoquinoline-3-carboxylate.▲ (USP 1-May-2023)

[i] Total impurities does not include quinapril related compound B and benzothiadiazine related compound A.

ADDITIONAL REQUIREMENTS

• **Packaging and Storage:** Preserve in well-closed containers, and protect from light. Store at controlled room temperature.

Change to read:

• **USP Reference Standards** ⟨11⟩

USP Benzothiadiazine Related Compound A RS

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

$C_6H_8ClN_3O_4S_2$ 285.73

USP Hydrochlorothiazide RS

USP Quinapril Hydrochloride RS

USP Quinapril Related Compound A RS

Ethyl[3*S*-[2(*R**),3a,11a beta]]-1,3,4,6,11,11a-hexahydro-3-methyl-1,4-dioxo-alpha-(2-phenylethyl)-2*H*-pyrazino[1,2-*b*]isoquinoline-2-acetate;

▲Also known as Ethyl (*S*)-2-{(3*S*,11a*S*)-3-methyl-1,4-dioxo-1,3,4,6,11,11a-hexahydro-2*H*-pyrazino[1,2-*b*]isoquinolin-2-yl}-4-phenylbutanoate.▲ (USP 1-May-2023)

$C_{25}H_{28}N_2O_4$ ▲420.51▲ (USP 1-May-2023)

USP Quinapril Related Compound B RS

3-Isoquinolinecarboxylic acid, 2-[2-[(1-carboxy-3-phenylpropyl)amino]-1-oxopropyl]-1,2,3,4-tetrahydro-, 3*S*-[2[*R**(*R**)],3*R**]]-;

▲Also known as (*S*)-2-{[(*S*)-1-Carboxy-3-phenylpropyl]-L-alanyl}-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid.▲ (USP 1-May-2023)

$C_{23}H_{26}N_2O_5$ ▲410.47▲ (USP 1-May-2023)

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

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

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