Status: Currently Official on 16-Feb-2025
Official Date: Official as of 01-Dec-2023
Document Type: USP Monographs
DocId: GUID-0BD3E17A-B017-4673-95C5-772F72CA4CF9_2_en-US
DOI: https://doi.org/10.31003/USPNF_M77920_02_01
DOI Ref: q13vc

Spironolactone and Hydrochlorothiazide Tablets

DEFINITION

Spironolactone and Hydrochlorothiazide Tablets contain NLT 90.0% and NMT 110.0% of the labeled amounts of spironolactone ($C_{24}H_{32}O_4S$) 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*.

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-Dec-2023)

ASSAY

Change to read:

• **Procedure**

▲Protect all solutions containing spironolactone and hydrochlorothiazide from light.

Solution A: Methanol and water (10:90)

Solution B: Methanol

Mobile phase: See *Table 1*.

Table 1

Time (min)	Solution A (%)	Solution B (%)
0	100	0
5	100	0
6	59	41
26	59	41
26.05	100	0
30	100	0

Diluent: Acetonitrile and water (50:50)

System suitability stock solution: 50 µg/mL each of USP Spironolactone Related Compound A RS and USP Benzothiadiazine Related Compound A RS in *Diluent*. Sonicate to dissolve if necessary.

System suitability solution: 0.1 mg/mL each of USP Spironolactone RS and USP Hydrochlorothiazide RS, and 1 µg/mL each of USP Spironolactone Related Compound A RS and USP Benzothiadiazine Related Compound A RS in *Diluent* prepared as follows. Transfer an appropriate amount of USP Spironolactone RS and USP Hydrochlorothiazide RS to a suitable volumetric flask. Add a suitable portion of the *System suitability stock solution* and dilute with *Diluent* to volume.

Standard solution: 0.1 mg/mL each of USP Spironolactone RS and USP Hydrochlorothiazide RS in *Diluent*. Sonicate to dissolve if necessary.

Sample stock solution: Nominally 0.5 mg/mL each of spironolactone and hydrochlorothiazide from Tablets prepared as follows. Transfer Tablets (NLT 10) to a suitable volumetric flask. Add *Diluent* to about 60% of the flask volume, sonicate for about 10 min, and maintain a cool

sonication bath temperature. Shake for about another 30 min and allow to cool to room temperature. Dilute with *Diluent* to volume.

Sample solution: Nominally 0.1 mg/mL each of spironolactone and hydrochlorothiazide from the *Sample stock solution* prepared as follows. Transfer 10.0 mL of the *Sample stock solution* to a 50-mL volumetric flask. Dilute with *Diluent* to volume. Pass a portion through a suitable filter of 0.45-µm pore size and discard the first 4 mL 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 190–400 nm.

Column: 4.6-mm × 15-cm; 2.7-µm packing L1

Temperatures

Autosampler: 5°

Column: 40°

Flow rate: 1.2 mL/min

Injection volume: 10 µL

System suitability

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

[NOTE—The relative retention times for benzothiadiazine related compound A, hydrochlorothiazide, spironolactone, and spironolactone related compound A are 0.7, 1.0, 4.0, and 4.4, respectively.]

Suitability requirements

Resolution: NLT 2.0 between benzothiadiazine related compound A and hydrochlorothiazide; NLT 2.0 between spironolactone and spironolactone related compound A, *System suitability solution*

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

Relative standard deviation: NMT 1.0% for hydrochlorothiazide and spironolactone, *Standard solution*▲ (USP 1-Dec-2023)

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentages of ▲the labeled amounts▲ (USP 1-Dec-2023) of spironolactone ($C_{24}H_{32}O_4S$) and 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 spironolactone or hydrochlorothiazide from the *Sample solution*

r_S = peak response of spironolactone or hydrochlorothiazide from the *Standard solution*

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

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

Acceptance criteria: 90.0%–110.0%

PERFORMANCE TESTS

Change to read:

• **DISSOLUTION ⟨711⟩**

Medium: 0.1 N hydrochloric acid containing 0.1% sodium dodecyl sulfate; 900 mL

Apparatus 2: 75 rpm

Time: 60 min

Solution A: Acetonitrile

Solution B: 4.5 g/L of monobasic potassium phosphate in water

Mobile phase: See *Table 2*.

Table 2

Time (min)	Solution A (%)	Solution B (%)
0	25	75

Time (min)	Solution A (%)	Solution B (%)
10	75	25
18	75	25
25	25	75

Standard solution: 12.5 µg/mL each of USP Spironolactone RS and USP Hydrochlorothiazide RS in a mixture of methanol and *Medium* ▲(50:50)▲ (USP 1-Dec-2023)

Sample solution: Transfer a 5.0-mL portion of the solution under test to a 10-mL volumetric flask, and dilute with methanol to volume.

Chromatographic system

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

Mode: LC

Detector: UV 254 nm

Column: 4.6-mm × 25-cm; ▲10-µm▲ (USP 1-Dec-2023) packing L1

Flow rate: 1 mL/min

Injection volume: 20 µL

System suitability

Sample: *Standard solution*

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

Suitability requirements

Resolution: NLT 2.0 between hydrochlorothiazide and spironolactone

Relative standard deviation: NMT 2.0% ▲each for hydrochlorothiazide and spironolactone▲ (USP 1-Dec-2023)

Analysis

Samples: *Standard solution* and *Sample solution*

▲Calculate the percentage of the labeled amounts of spironolactone ($C_{24}H_{32}O_4S$) and hydrochlorothiazide ($C_7H_8ClN_3O_4S_2$) dissolved:

$$\text{Result} = (r_U/r_S) \times C_S \times V \times D \times (1/L) \times 100$$

r_U = peak response of spironolactone or hydrochlorothiazide from the *Sample solution*

r_S = peak response of spironolactone or hydrochlorothiazide from the *Standard solution*

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

V = volume of *Medium*, 900 mL

D = dilution factor for the *Sample solution*

L = label claim of spironolactone or hydrochlorothiazide (mg/Tablet)

▲ (USP 1-Dec-2023)

Tolerances: NLT 75% (Q) each of the labeled amounts of spironolactone ($C_{24}H_{32}O_4S$) and hydrochlorothiazide ($C_7H_8ClN_3O_4S_2$) is dissolved.

Change to read:

• **UNIFORMITY OF DOSAGE UNITS ⟨905⟩:** Meet the requirements ▲▲ (USP 1-Dec-2023)

Add the following:

▲IMPURITIES

• **ORGANIC IMPURITIES**

Protect all solutions containing spironolactone and hydrochlorothiazide from light.

Solution A, Solution B, Diluent, System suitability stock solution, and **System suitability solution:** Prepare as directed in the *Assay*.

Mobile phase: See *Table 3*.

Table 3

Time (min)	Solution A (%)	Solution B (%)
0	100	0
5	100	0
14	60	40
34	60	40
41	20	80
46	20	80
51.5	100	0
60	100	0

Sensitivity solution: 0.5 µg/mL of USP Hydrochlorothiazide RS in *Diluent*. Sonicate to dissolve if necessary.

Standard stock solution: Use *Standard solution* from the *Assay*.

Standard solution: 5 µg/mL each of USP Benzothiadiazine Related Compound A RS, USP Spironolactone Related Compound A RS, USP Spironolactone RS, and USP Hydrochlorothiazide RS in *Diluent* prepared as follows. Transfer a suitable portion of the *Standard stock solution* to a suitable volumetric flask. Add a suitable portion of the *System suitability stock solution* and dilute with *Diluent* to volume.

Sample solution: Nominally 500 µg/mL each of spironolactone and hydrochlorothiazide in *Diluent*, prepared as follows. Transfer a portion of finely powdered Tablets (NLT 20), equivalent to 250 mg each of spironolactone and hydrochlorothiazide, to a suitable volumetric flask. Add *Diluent* to about 60% of the flask volume, sonicate for about 10 min, and maintain a cool sonication bath temperature. Shake for about another 30 min and dilute with *Diluent* to volume. Pass a portion through a suitable filter of 0.2-µm pore size and discard the first 4 mL of the filtrate. [NOTE—It is recommended to store the *Sample solution* in a refrigerator and use within 6 h.]

Chromatographic system

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

Mode: LC

Detector: UV 254 nm

Columns

Guard: 2.1-mm × 5-mm; 1.6-µm packing L1

Analytical: 2.1-mm × 15-cm; 1.6-µm packing L1

Temperatures

Autosampler: 5°

Column: 40°

Flow rate: 0.3 mL/min

Injection volume: 2 µL

System suitability

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

[NOTE—The relative retention times in *Table 4* are provided as information that could aid in peak assignment.]

Table 4

Name	Relative Retention Time
Benzothiadiazine related compound A	0.7
Hydrochlorothiazide	1.0
Spironolactone related compound B[a]	5.6

Name	Relative Retention Time
Spironolactone	5.7
Spironolactone related compound A	6.1
Spironolactone related compound C[b]	6.8
7-Epispironolactone[c]	7.0
Spironolactone related compound D[d]	7.3

[a] (2′*R*)-7α-(Acetylthio)-5′*H*-spiro[androst-4-ene-17,2′-furan]-3,5′-dione.

[b] (2′*R*)-3′,4′-Dihydro-5′*H*-spiro[androst-4-ene-17,2′-furan]-3,5′-dione.

[c] (2′*R*)-7β-(Acetylthio)-3′,4′-dihydro-5′*H*-spiro[androst-4-ene-17,2′-furan]-3,5′-dione.

[d] (2′*R*)-7α-(Acetyldisulfanyl)-3′,4′-dihydro-5′*H*-spiro[androst-4-ene-17,2′-furan]-3,5′-dione.

Suitability requirements

Resolution: NLT 2.0 between benzothiadiazine related compound A and hydrochlorothiazide; NLT 2.0 between spironolactone and spironolactone related compound A, *System suitability solution*

Relative standard deviation: NMT 5.0% each for benzothiadiazine related compound A, hydrochlorothiazide, spironolactone, and spironolactone related compound A, *Standard solution*

Signal-to-noise ratio: NLT 10, *Sensitivity solution*

Analysis

Samples: *Standard solution* and *Sample solution*

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* (µg/mL)

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

Calculate the percentage of spironolactone 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 spironolactone related compound A from the *Sample solution*

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

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

C_U = nominal concentration of spironolactone in the *Sample solution* (µg/mL)

Calculate the percentage of any unspecified degradation product in the portion of Tablets taken:

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

r_U = peak response of any unspecified degradation product 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* (µg/mL)

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

Acceptance criteria: See *Table 5*. The reporting threshold is 0.1%.

Table 5

Name	Acceptance Criteria, NMT (%)
Benzothiadiazine related compound A	1.0
Spironolactone related compound A	1.0
Any unspecified degradation product	0.2
Total degradation products[a]	2.0

[a] Excluding benzothiadiazine related compound A.

▲ (USP 1-Dec-2023)

ADDITIONAL REQUIREMENTS

Change to read:

• **Packaging and Storage:** Preserve in tight, light-resistant containers. ▲Store at controlled room temperature.▲ (USP 1-Dec-2023)

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 1-Dec-2023)

USP Hydrochlorothiazide RS

USP Spironolactone RS

▲ USP Spironolactone Related Compound A RS

(2′*R*)-3′,4′-Dihydro-5′*H*-spiro[androst-4,6-diene-17,2′-furan]-3,5′-dione.

$C_{22}H_{28}O_3$ 340.46▲ (USP 1-Dec-2023)

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

Topic/Question	Contact	Expert Committee
SPIRONOLACTONE 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. 48(4)

Current DocID: GUID-0BD3E17A-B017-4673-95C5-772F72CA4CF9_2_en-US

DOI: https://doi.org/10.31003/USPNF_M77920_02_01

DOI ref: q13vc