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Moexipril Hydrochloride and Hydrochlorothiazide Tablets

DEFINITION

Moexipril Hydrochloride and Hydrochlorothiazide Tablets contain NLT 90.0% and NMT 110.0% each of the labeled amounts of moexipril hydrochloride ($C_{27}H_{34}N_2O_7 \cdot HCl$) 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*.

Add the following:

▲• **B.** The UV spectra of the major peaks of the *Diluted sample solution* correspond to those of the *Diluted standard solution*, as obtained in the *Assay*.▲ (USP 1-Aug-2020)

ASSAY

Change to read:

• **Procedure**

Buffer: 0.01 M potassium dihydrogen phosphate

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

Diluent: Acetonitrile and water (30:70)

Standard solution: Prepare solutions of USP Moexipril Hydrochloride RS and USP Hydrochlorothiazide RS in *Diluent*, of concentrations stated in *Table 1*. Initially add *Diluent* to 70% of the total volume, sonicate to dissolve, and then dilute with *Diluent* to volume.

Table 1

Tablet Strength Moexipril Hydrochloride/ Hydrochlorothiazide (mg/mg)	Concentration of Moexipril Hydrochloride (mg/mL)	Concentration of Hydrochlorothiazide (mg/mL)
7.5/12.5	0.06	0.1
15/12.5	0.06	0.05
15/25	0.06	0.1

▲**Diluted standard solution:** *Standard solution* and *Diluent* (50:50)▲ (USP 1-Aug-2020)

Sample solution: The nominal concentrations of moexipril and hydrochlorothiazide in mg/mL given in *Table 1* prepared as follows from powdered Tablets (NLT 20). Initially add *Diluent* to about 60% of the total volume, sonicate for 45 min with intermittent shaking, and then dilute with *Diluent* to volume. Pass through a suitable filter of 0.45-µm pore size.

▲**Diluted sample solution:** *Sample solution* and *Diluent* (50:50)▲ (USP 1-Aug-2020)

Chromatographic system

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

Mode: LC

Detector: UV 210 nm. ▲For *Identification B*, use a diode array detector in the range of 200–400 nm.▲ (USP 1-Aug-2020)

Column: 4.6-mm × 25-cm; 5-µm packing L7

Column temperature: 30°

Flow rate: 1 mL/min

Injection volume: 20 µL

Run time: ▲NLT▲ (USP 1-Aug-2020) 2.2 times the retention time of the moexipril peak

System suitability

Sample: *Standard solution*

▲[NOTE—The relative retention times for hydrochlorothiazide and moexipril are 0.43 and 1.00, respectively.]▲ (USP 1-AUG-2020)

Suitability requirements

▲▲ (USP 1-Aug-2020)

Tailing factor: NMT 2.0 for both the moexipril and hydrochlorothiazide peaks

Relative standard deviation: NMT 2.0% for both the moexipril and hydrochlorothiazide peaks

Analysis

Samples: *Standard solution*, ▲*Diluted standard solution*,▲ (USP 1-Aug-2020) *Sample solution*, and ▲*Diluted sample solution*

[NOTE—The *Diluted standard solution* and *Diluted sample solution* are used for *Identification B*.]▲ (USP 1-AUG-2020)

Calculate the percentage of the labeled amounts of moexipril hydrochloride ($C_{27}H_{34}N_2O_7 \cdot HCl$) 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 moexipril or hydrochlorothiazide from the *Sample solution*

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

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

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

Acceptance criteria: 90.0%–110.0% each of the labeled amounts of moexipril hydrochloride and hydrochlorothiazide

PERFORMANCE TESTS

Change to read:

• **DISSOLUTION** ⟨711⟩

Medium: 0.1 N hydrochloric acid; 900 mL

Apparatus 2: 50 rpm

Time: 15 min

Buffer, Mobile phase, ▲▲ (USP 1-Aug-2020) **Chromatographic system,** and **System suitability:** Proceed as directed in the *Assay*.

Standard solution: Prepare solutions of USP Moexipril Hydrochloride RS and USP Hydrochlorothiazide RS in *Medium* of concentrations stated in *Table 2*.

Table 2

Tablet Strength Moexipril Hydrochloride/ Hydrochlorothiazide (mg/mg)	Concentration of USP Moexipril Hydrochloride RS (µg/mL)	Concentration of USP Hydrochlorothiazide RS (µg/mL)
7.5/12.5	8	14
15/12.5	16	14
15/25	16	28

Sample solution: Pass a portion of the solution under test through a suitable filter of 0.45-µm pore size, discarding the first 2–3 mL.

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amounts of moexipril hydrochloride ($C_{27}H_{34}N_2O_7 \cdot HCl$) and hydrochlorothiazide ($C_7H_8ClN_3O_4S_2$) dissolved:

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

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

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

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

V = volume of *Medium*, 900 mL

L = label claim for moexipril hydrochloride or hydrochlorothiazide (mg/Tablet)

Tolerances: NLT 70% (*Q*) of the labeled amounts each of moexipril hydrochloride ($C_{27}H_{34}N_2O_7 \cdot HCl$) and hydrochlorothiazide ($C_7H_8ClN_3O_4S_2$) are dissolved.

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

IMPURITIES

Change to read:

• **Organic Impurities**

Solution A: Add 1 mL of trifluoroacetic acid to 4 L of water.

Solution B: Acetonitrile and tetrahydrofuran (90:10)

Mobile phase: See *Table 3*.

Table 3

Time (min)	Solution A (%)	Solution B (%)
0	95	5
50	30	70
60	95	5
70	95	5

Diluent: Prepare as directed in the *Assay*.

System suitability solution: 1.2 mg/mL of USP Moexipril Hydrochloride RS, 2 mg/mL of USP Hydrochlorothiazide RS, and 2.4 µg/mL of USP Moexipril Related Compound G RS in *Diluent*. Initially add *Diluent* to 70% of the total volume, sonicate to dissolve, and then dilute with *Diluent* to volume.

Standard solution: 1.2 µg/mL of USP Moexipril Hydrochloride RS, 12 µg/mL each of USP Moexipril Related Compound A RS and USP Moexipril Related Compound B RS, 2 µg/mL of USP Hydrochlorothiazide RS, and 40 µg/mL each of USP Benzothiadiazine Related Compound A RS and USP Chlorothiazide RS in *Diluent*. Initially add *Diluent* to 70% of the total volume, sonicate to dissolve, and then dilute with *Diluent* to volume.

Sample solution: The nominal concentrations of moexipril and hydrochlorothiazide in mg/mL given in *Table 4* prepared as follows. Initially add *Diluent* to 70% of the total volume, and sonicate for 15 min with intermittent shaking in ice cold water. Dilute with *Diluent* to volume, and pass through a suitable filter of 0.45-µm pore size.

Table 4

Tablet Strength Moexipril Hydrochloride/ Hydrochlorothiazide (mg/mg)	Number of Tablets (NLT)	Nominal Concentration of Moexipril Hydrochloride (mg/mL)	Nominal Concentration of Hydrochlorothiazide (mg/mL)
7.5/12.5	20	1.2	2
15/12.5	10	1.8	1.5
15/25	10	1.2	2

Chromatographic system

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

Mode: LC

Detector: UV 210 nm

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

Column temperature: 30°

Flow rate: 1 mL/min

Injection volume: 10 µL

System suitability

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

▲[Note—See *Table 5* for the relative retention times.]▲ (USP 1-Aug-2020)

Suitability requirements

Resolution: NLT 2.5 between the moexipril and moexipril related compound G peaks, *System suitability solution*

Tailing factor: NMT 2.0 for both the moexipril and hydrochlorothiazide peaks, *Standard solution*

Relative standard deviation: NMT 5.0% for both the moexipril and hydrochlorothiazide peaks, *Standard solution*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of moexipril related compound A ▲or▲ (USP 1-Aug-2020) moexipril 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 moexipril related compound A or moexipril related compound B from the *Sample solution*

r_S = peak response of ▲moexipril related compound A or moexipril related compound B▲ (USP 1-Aug-2020) from the *Standard solution*

C_S = concentration of USP Moexipril Related Compound A RS▲or▲ (USP 1-Aug-2020) USP Moexipril Related Compound B RS in the *Standard solution* (mg/mL)

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

Calculate the percentage of benzothiadiazine related compound A or chlorothiazide 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 or chlorothiazide from the *Sample solution*

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

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

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

Calculate the percentage of any other individual impurity 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 other individual impurity from the *Sample solution*

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

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

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

Acceptance criteria: See *Table 5*.

Table 5

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Moexipril related compound E[a,b]	0.31	—
Benzothiadiazine related compound A▲▲ (USP 1-Aug-2020)	0.47	1.0
Chlorothiazide▲▲ (USP 1-Aug-2020)	0.53	0.5
Hydrochlorothiazide	0.57	—
Moexipril related compound F[b,c]	0.77	—
5-Chlorohydrochlorothiazide[b,d]	0.82	—

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Moexipril related compound A▲▲ (USP 1-Aug-2020)	0.85	1.0
Moexipril related compound G[b]▲▲ (USP 1-Aug-2020)	0.94	—
Moexipril	1.00	—
Moexipril related compound D[b,e]	1.17	—
Moexipril related compound C[b,f]	1.27	—
Moexipril related compound B▲▲ (USP 1-Aug-2020)	1.43	1.5
Any other individual unspecified impurity	—	0.2
Total impurities[g]	—	4.0

▲ ▲ (USP 1-Aug-2020)

▲ ▲ (USP 1-Aug-2020)

▲ ▲ (USP 1-Aug-2020)

[a] (*S*)-6,7-Dimethoxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid.

[b] Process-related impurity controlled in the drug substance.

[c] (*S*)-2-[(*S*)-1-Ethoxy-1-oxo-4-phenylbutan-2-ylamino]propanoic acid.

[d] ▲5,6-Dichloro-3,4-dihydro-2*H*-benzothiadiazine-7-sulfonamide 1,1-dioxide.▲ (USP 1-Aug-2020)

[e] (*S*)-2-{(*S*)-2-[(*S*)-4-Cyclohexyl-1-ethoxy-1-oxobutan-2-ylamino]propanoyl}-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid.

[f] (*S*)-*tert*-Butyl 2-{(*S*)-2-[(*S*)-1-ethoxy-1-oxo-4-phenylbutan-2-ylamino]propanoyl}-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylate.

[g] Total impurities is a sum total of all specified and unspecified impurities.

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 Chlorothiazide RS

▲6-Chloro-2*H*-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide.▲ (USP 1-Aug-2020)

$C_7H_6ClN_3O_4S_2$ 295.73

USP Hydrochlorothiazide RS

USP Moexipril Hydrochloride RS

USP Moexipril Related Compound A RS

(3*S*)-2-{(2*S*)-*N*-[(1*S*)-1-Carboxy-3-phenylpropyl]alanyl}-1,2,3,4-tetrahydro-6,7-dimethoxy-3-isoquinolinecarboxylic acid.

$C_{25}H_{30}N_2O_7$ 470.51

USP Moexipril Related Compound B RS

(*S*)-Ethyl 2-{(3*S*,11a*S*)-8,9-dimethoxy-3-methyl-1,4-dioxo-3,4-dihydro-1*H*-pyrazino[1,2-b]isoquinolin-2(6*H*,11*H*,11a*H*)-yl}-4-phenylbutanoate.

$C_{27}H_{32}N_2O_6$ 480.55

USP Moexipril Related Compound G RS

(*S*)-6,7-Dimethoxy-2-{(*S*)-2-[(*S*)-1-methoxy-1-oxo-4-phenylbutan-2-ylamino]propanoyl}-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid.

$C_{26}H_{32}N_2O_7$ 484.54

Topic/Question	Contact	Expert Committee
MOEXIPRIL HYDROCHLORIDE AND HYDROCHLOROTHIAZIDE TABLETS	Documentary Standards Support	SM22020 Small Molecules 2

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