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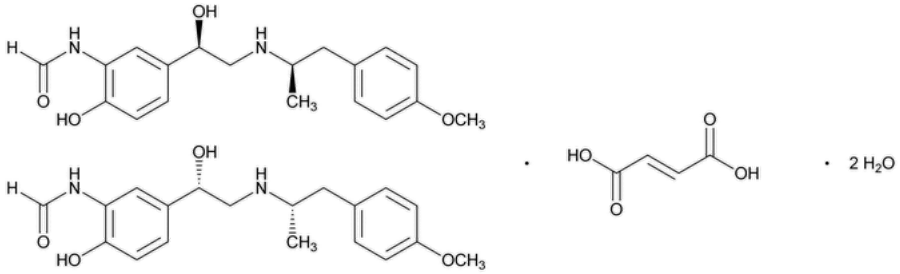
Formoterol Fumarate



$(C_{19}H_{24}N_2O_4)_2 \cdot C_4H_4O_4 \cdot 2H_2O$ 840.92

Formamide, *N*-[2-hydroxy-5-[1-hydroxy-2-[[1-(4-methoxyphenyl)propan-2-yl]amino]ethyl]phenyl], (*R**,*R**)-, fumarate (2:1) (salt), dihydrate; (±)-2'-Hydroxy-5'-[(*R**)-1-hydroxy-2-[[(*R**)-*p*-methoxy-α-methylphenethyl]amino]ethyl]formanilide fumarate (2:1) (salt), dihydrate CAS RN®: 183814-30-4; UNII: W34SHF8J2K.

Anhydrous

$(C_{19}H_{24}N_2O_4)_2 \cdot C_4H_4O_4$ 804.89 CAS RN®: 43229-80-7.

DEFINITION

Formoterol Fumarate contains NLT 98.5% and NMT 101.5% of formoterol fumarate [$(C_{19}H_{24}N_2O_4)_2 \cdot C_4H_4O_4$], calculated on the anhydrous basis.

IDENTIFICATION

• **A. Spectroscopic Identification Tests ⟨197⟩, *Infrared Spectroscopy*:** 197K or 197A

• **B.** The retention time of the formoterol peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay*.

ASSAY

• **Procedure**

Protect solutions of formoterol fumarate from light.

Buffer: 6.1 g/L of monobasic sodium phosphate and 1.0 g/L of dibasic sodium phosphate dihydrate in water. [Note—The pH is 6.0 ± 0.1.]

Solution A: 3.7 g/L of monobasic sodium phosphate and 0.35 g/L of phosphoric acid in water. [Note—The pH is 3.1 ± 0.1.]

Solution B: Acetonitrile

Mobile phase: See *Table 1*.

Table 1

Time (min)	Solution A (%)	Solution B (%)
0	84	16
10	84	16
12.7	30	70
12.8	84	16
18	84	16

Diluent: Acetonitrile and *Buffer* (16:84)

Standard solution: 0.2 mg/mL of USP Formoterol Fumarate RS in *Diluent*

Sample solution: 0.2 mg/mL of Formoterol Fumarate in *Diluent*

Chromatographic system

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

Mode: LC

Detector: UV 214 nm

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

Flow rate: 1 mL/min

Injection volume: 10 µL

System suitability

Sample: *Standard solution*

Suitability requirements

Tailing factor: NMT 2.0

Relative standard deviation: NMT 0.73%

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of formoterol fumarate $[(C_{19}H_{24}N_2O_4)_2 \cdot C_4H_4O_4]$ in the portion of Formoterol Fumarate taken:

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

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

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

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

C_U = concentration of Formoterol Fumarate in the *Sample solution* (mg/mL)

Acceptance criteria: 98.5%–101.5% on the anhydrous basis

IMPURITIES

• **Residue on Ignition ⟨281⟩**

Sample: 1 g

Acceptance criteria: NMT 0.1%

Change to read:

• **Organic Impurities**

Protect solutions of formoterol fumarate from light.

Buffer, Solution A, Solution B, and **Diluent:** Prepare as directed in the *Assay*.

Mobile phase: See *Table 2*.

Table 2

Time (min)	Solution A (%)	Solution B (%)
0	84	16
10	84	16
37	30	70
40	84	16
55	84	16

System suitability solution: 0.2 mg/mL of USP Formoterol Fumarate RS and 2 µg/mL each of USP Formoterol Related Compound A RS, USP Formoterol Related Compound C RS, and USP Formoterol Related Compound D RS in *Diluent*. Sonicate to dissolve prior to final dilution.

Sensitivity solution: 0.1 µg/mL of USP Formoterol Fumarate RS in *Diluent*

Sample solution: 0.2 mg/mL of Formoterol Fumarate in *Diluent*. Sonicate to dissolve before final dilution.

Chromatographic system

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

Mode: LC

Detector: UV 214 nm

Column: 4.6-mm × 15-cm; packing L7

Flow rate: 1 mL/min

Injection volume: 20 µL

System suitability

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

[Note—The relative retention times for the peaks are given in *Table 3*.]

Suitability requirements

Resolution: NLT 2.0 between formoterol and formoterol related compound C; and ▲NLT 1.2▲ (USP 1-May-2022) between formoterol related compound C and formoterol related compound D, *System suitability solution*

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

Analysis

Sample: *Sample solution*

Calculate the percentage of each impurity in the portion of Formoterol Fumarate taken:

$$\text{Result} = (r_U/r_T) \times (1/F) \times 100$$

r_U = peak response of each impurity from the *Sample solution*

r_T = sum of the responses of all peaks from the *Sample solution*

F = relative response factor for each peak (see *Table 3*)

Acceptance criteria: See *Table 3*. The reporting threshold is 0.05%.

Table 3

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
	0.15	—	—
▲Fumaric acid[a]	0.17	—	—▲ (USP 1-May-2022)
2-Aminopropyl anisol[b]	0.4	1.0	0.1
Formoterol related compound A	0.5	0.57	0.3
Desmethyl formoterol[c]	0.7	1.0	0.2
Formoterol	1.0	—	—
Formoterol related compound C	1.2	1.0	0.2
Formoterol related compound D	1.3	1.0	0.2
3-Methyl formoterol[d]	1.8	1.0	0.1
Formoterol dimer[e,f]	2.0	1.0	0.2
N-Benzyl formoterol[g]	2.2	1.0	0.1
Any individual unspecified impurity	—	1.0	0.10
Total impurities	—	—	0.5

[a] Salt counter ion included for identification only, not to be reported or included in the total impurities.

[b] 1-(4-Methoxyphenyl)propan-2-amine.

[c] *N*-(2-Hydroxy-5-{1-hydroxy-2-[(4-methoxyphenethyl)amino]ethyl}phenyl)formamide.

[d] *N*-[2-Hydroxy-5-(1-hydroxy-2-{[1-(4-methoxy-3-methylphenyl)propan-2-yl]amino}ethyl)phenyl]formamide.

[e] *N*-[2-Hydroxy-5-(1-{[2-hydroxy-5-(1-hydroxy-2-{[1-(4-methoxyphenyl)propan-2-yl]amino}ethyl)phenyl]amino}-2-{[1-(4-methoxyphenyl)propan-2-yl]amino}ethyl)phenyl]formamide.

[f] When present in the chromatogram, the formoterol dimer diasteromers will appear as multiple overlapped peaks, for which the total peak area is to be assessed.

[g] *N*-{5-[(*RS*)-2-{Benzyl[(*RS*)-1-(4-methoxyphenyl)propan-2-yl]amino}-1-hydroxyethyl]-2-hydroxyphenyl}formamide.

Change to read:

- **Limit of Formoterol Related Compound I**

Buffer: 4.2 g/L of tribasic potassium phosphate. Adjust with potassium hydroxide or phosphoric acid to a pH of 12.0 ± 0.1.

Mobile phase: Acetonitrile and *Buffer* (12:88)

System suitability solution: ▲100 µg/mL of USP Formoterol Fumarate RS and 1 µg/mL of USP Formoterol Related Compound I RS▲ (USP 1-May-2022) in water

▲**Standard solution:** 0.3 µg/mL of USP Formoterol Fumarate RS in water▲ (USP 1-May-2022)

Sample solution: ▲100 µg/mL▲ (USP 1-May-2022) of Formoterol Fumarate in water

▲▲ (USP 1-May-2022)

Chromatographic system

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

Mode: LC

Detector: UV 225 nm

Column: 4.6-mm × 15-cm; ▲5-µm▲ (USP 1-May-2022) packing L67

Flow rate: 0.5 mL/min

Injection volume: 20 µL

Run time: NLT 2 times the retention time of formoterol

System suitability

Samples: *System suitability solution*▲and *Standard solution*▲ (USP 1-May-2022)

[Note—The relative retention times for formoterol and formoterol related compound I are 1.0 and 1.17, respectively.]

Suitability requirements

Peak-to-valley ratio: NLT 2.5 for formoterol related compound I and formoterol, *System suitability solution*

▲**Relative standard deviation:** NMT 5.0%, *Standard solution*▲ (USP 1-May-2022)

Analysis

Samples: ▲*Standard solution* and▲ (USP 1-May-2022) *Sample solution*

▲Calculate the percentage of formoterol related compound I in the portion of Formoterol Fumarate taken:

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

r_U = peak response of formoterol related compound I from the *Sample solution*

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

C_S = concentration of USP Formoterol Fumarate RS in the *Standard solution* (µg/mL)

C_U = concentration of Formoterol Fumarate in the *Sample solution* (µg/mL)▲ (USP 1-May-2022)

Acceptance criteria: NMT 0.3% ▲▲ (USP 1-May-2022)

SPECIFIC TESTS

- **pH** ⟨791⟩

Sample solution: 1 mg/mL in water

Acceptance criteria: 5.5–6.5

- **Water Determination** ⟨921⟩, *Method I*: 4.0%–5.0%

ADDITIONAL REQUIREMENTS

- **Packaging and Storage:** Preserve in well-closed light-resistant containers.

Change to read:

- **USP Reference Standards** ⟨11⟩

USP Formoterol Fumarate RS

▲▲ (USP 1-May-2022)

USP Formoterol Related Compound A RS

2-Amino-4-(1-hydroxy-2-((1-(4-methoxyphenyl)propan-2-yl)amino)ethyl)phenol.

$C_{18}H_{24}N_2O_3$ ▲316.40▲ (USP 1-May-2022)

USP Formoterol Related Compound C RS

N-(2-Hydroxy-5-(1-hydroxy-2-{[1-(4-methoxyphenyl)propan-2-yl]amino}ethyl)phenyl)acetamide fumarate (2:1) salt.

$(C_{20}H_{26}N_2O_4)_2 \cdot C_4H_4O_4$ 832.95

USP Formoterol Related Compound D RS

N-(2-Hydroxy-5-(1-hydroxy-2-{[1-(4-methoxyphenyl)propan-2-yl](methyl)amino}ethyl)phenyl)formamide fumarate (2:1) salt.

$(C_{20}H_{26}N_2O_4)_2 \cdot C_4H_4O_4$ 832.95

▲ USP Formoterol Related Compound I RS

N-(2-Hydroxy-5-[(*RS*)-1-hydroxy-2-{[(*SR*)-1-(4-methoxyphenyl)propan-2-yl]amino}ethyl]phenyl)formamide.

$C_{19}H_{24}N_2O_4$ 344.41 ▲ (USP 1-May-2022)

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

Topic/Question	Contact	Expert Committee
FORMOTEROL FUMARATE	Documentary Standards Support	SM52020 Small Molecules 5

Chromatographic Database Information: Chromatographic Database

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