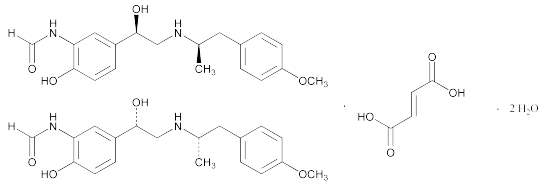
Assay—Into a 100-mL volumetric flask containing 2.5 mL of water and 1 mL of sodium hydroxide TS 2, introduce 1.0 g of the Solution to be examined, shake, and dilute with water to 100.0 mL. To 10.0 mL of the solution add 30.0 mL of 0.1 N iodine VS. Mix, and add 10 mL of sodium hydroxide TS 2. After 15 minutes, add 25 mL of diluted sulfuric acid and 4 mL of starch TS. Titrate with 0.1 N sodium thiosulphate VS. Each 1 mL of 0.05 M iodine is equivalent to 1.501 mg of CH_2O.

Formoterol Fumarate



$(C_{19}H_{24}N_2O_4)_2 \cdot C_4H_4O_4 \cdot 2H_2O$ 840.91

(±)-2′-Hydroxy-5′-[(*R**)-1-hydroxy-2-[[(*R**)-*p*-methoxy-α-methylphenethyl]amino]ethyl]formanilide fumarate (2:1) (salt), dihydrate [43229-80-7].

» Formoterol Fumarate contains not less than 98.5 percent and not more than 101.5 per cent of $(C_{19}H_{24}N_2O_4)_2 \cdot C_4H_4O_4$, calculated on the anhydrous basis.

Packaging and storage—Preserve in well-closed, light-resistant containers.

Labeling—The labeling states with which *Content of related compound I* the test article complies if a test other than *Content of related compound I, Test 1* is used.

USP Reference standards ⟨11⟩**—**
USP Formoterol Fumarate RS
USP Formoterol Fumarate System Suitability Mixture RS
It is a mixture of USP Formoterol Fumarate RS and formoterol related compounds A, B, C, D, E, F, G, and H.
Formoterol related compound A: 1-(3-Amino-4-hydroxyphenyl)-2-[[2-(4-methoxyphenyl)-1-methylethyl]amino]ethanol.
Formoterol related compound B: N-[2-Hydroxy-5-[(1*RS*)-1-hydroxy-2-[[2-(4-methoxyphenyl)ethyl]amino]ethyl]phenyl]formamide.
Formoterol related compound C: N-[2-Hydroxy-5-[1-hydroxy-2-[[2-(4-methoxyphenyl)-1-methylethyl]amino]ethyl]phenyl]acetamide.
Formoterol related compound D: N-[2-Hydroxy-5-[1-hydroxy-2-[methyl[2-(4-methoxyphenyl)-1-methylethyl]amino]ethyl]phenyl]formamide.
Formoterol related compound E: N-[2-Hydroxy-5-[1-hydroxy-2-[[2-(4-methoxy-3-methylphenyl)-1-methylethyl]amino]ethyl]phenyl]formamide.
Formoterol related compound F: N-[2-Hydroxy-5-[1-[[2-hydroxy-5-[1-hydroxy-2-[[2-(4-methoxyphenyl)-1-methylethyl]amino]ethyl]phenyl]amino]-2-[[2-(4-methoxyphenyl)-1-methylethyl]amino]ethyl]phenyl]formamide.
Formoterol related compound G: (2*RS*)-1-(4-Methoxyphenyl)propan-2-amine.
Formoterol related compound H: N-[5-[(1*RS*)-2-[Benzyl[(1*RS*)-2-(4-methoxyphenyl)-1-methylethyl]amino]-1-hydroxyethyl]-2-hydroxyphenyl]formamide (monobenzyl analogue).
USP Formoterol Resolution Mixture RS
This standard is a mixture of formoterol and formoterol fumarate impurity I.
Impurity I: N-[2-hydroxy-5-[(1*RS*)-1-hydroxy-2-[[(1*SR*)-2-(4-methoxyphenyl)-1-methylethyl]amino]ethyl]phenyl]formamide fumarate salt (2:1)(diastereoisomer).

Identification, *Infrared Absorption* ⟨197K⟩**.**

Optical rotation, *Angular Rotation* ⟨781A⟩**:** between –0.10° and +0.10°.

Test solution: 10 mg per mL, in methanol.

pH ⟨791⟩**:** between 5.5 and 6.5, in a solution in water containing 1 mg per mL.

Water, *Method I* ⟨921⟩**:** between 4.0% and 5.0%.

Residue on ignition ⟨281⟩**:** not more than 0.1%, determined on 1 g.

Heavy metals, *Method II* ⟨231⟩**:** not more than 0.002%.

Related compounds—

Solution A—Dissolve 3.73 g of sodium dihydrogen phosphate monohydrate and 0.35 g of phosphoric acid in water, dilute with water to 1000 mL, and mix. The pH of this solution is 3.1 ± 0.1.

Solution B—Use acetonitrile.

Mobile phase—Use variable mixtures of *Solution A* and *Solution B* as directed for *Chromatographic system.* Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Solution C—Transfer 6.10 g of sodium dihydrogen phosphate monohydrate and 1.03 g of disodium hydrogen phosphate dihydrate to a 1000-mL volumetric flask, add 500 mL of water, and dissolve. Dilute with water to volume, and mix. The pH is 6.0 ± 0.1.

Diluent—Prepare a filtered and degassed mixture of *Solution C* and acetonitrile (84:16, v/v).

System suitability solution—Transfer about 5 mg of USP Formoterol Fumarate System Suitability Mixture RS (containing formoterol fumarate, and formoterol related compounds A, B, C, D, E, F, G, and H), accurately weighed, to a 25-mL volumetric flask, add 10 mL of *Diluent,* and sonicate to dissolve. Dilute with *Diluent* to volume, and mix.

Test solution—Transfer about 20.0 mg of Formoterol Fumarate, accurately weighed, to a 100-mL volumetric flask, add 50 mL of *Diluent,* and sonicate to dissolve. Dilute with *Diluent* to volume, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 214-nm detector and a 4.6-mm × 15-cm column that contains packing L7. The flow rate is about 1.0 mL per minute. The chromatograph is programmed as follows.

Time (minutes)	*Solution A* (%)	*Solution B* (%)	Elution
0	84	16	equilibration
0–10	84	16	isocratic
10–37	84→30	16→70	linear gradient
37–40	30→84	70→16	linear gradient
40–55	84	16	isocratic

Chromatograph the *System suitability solution,* and record the peak responses as directed for *Procedure:* the resolution, *R,* between formoterol related compound G and formoterol related compound A is not less than 1.5; the peak-to-valley ratio (H_P / H_V) of formoterol related compound C and formoterol is not less than 2.5, where H_P is the height above the baseline of the peak due to formoterol related compound C, and H_V is the height above the baseline of the lowest point of the curve separating this peak from the peak due to formoterol; and the relative retention times and limits are as provided in *Table 1.*

Table 1

Related Compound	Relative Retention Time	Relative Response Factor (*F*)	Limit (%)
G[a]	0.4	2.64	0.1
A[b]	0.5	1.75	0.3
B[c]	0.7	1.00	0.2
C[d]	1.2	1.10	0.2
D[e]	1.3	1.12	0.2
E[f]	1.8	0.67	0.1
F[g]	2.0	1.00	0.2
H[h]	2.2	1.24	0.1
Any other individual impurity			0.1
Total unspecified impurities			0.2
Total impurities			0.5

[a](2*RS*)-1-(4-Methoxyphenyl)propan-2-amine.
[b]1-(3-Amino-4-hydroxyphenyl)-2-[[2-(4-methoxyphenyl)-1-methylethyl]amino]ethanol.
[c]*N*-[2-Hydroxy-5-[(1*RS*)-1-hydroxy-2-[[2-(4-methoxyphenyl)ethyl]amino]ethyl]phenyl]formamide.
[d]*N*-[2-Hydroxy-5-[1-hydroxy-2-[[2-(4-methoxyphenyl)-1-methylethyl]amino]ethyl]phenyl]acetamide.
[e]*N*-[2-Hydroxy-5-[1-hydroxy-2-[methyl[2-(4-methoxyphenyl)-1-methylethyl]amino]ethyl]phenyl]formamide.
[f]*N*-[2-Hydroxy-5-[1-hydroxy-2-[[2-(4-methoxy-3-methylphenyl)-1-methylethyl]amino]ethyl]phenyl]formamide.
[g]*N*-[2-Hydroxy-5-[1-[[2-hydroxy-5-[1-hydroxy-2-[[2-(4-methoxyphenyl)-1-methylethyl]amino]ethyl]phenyl]amino]-2-[[2-(4-methoxyphenyl)-1-methylethyl]amino]ethyl]phenyl]formamide.
[h]*N*-[5-[(1*RS*)-2-[Benzyl[(1*RS*)-2-(4-methoxyphenyl)-1-methylethyl]amino]-1-hydroxyethyl]-2-hydroxyphenyl]formamide (monobenzyl analogue).

Procedure—Separately inject equal volumes (about 20 µL) of the *System suitability solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure all of the peak responses. Disregard any peak representing less than 0.05%. Calculate the per centage of each formoterol related compound in the portion of Formoterol Fumarate taken by the formula:

$$100F(r_i / r_s)$$

in which F is the relative response factor for each formoterol related compound according to *Table 1*; r_i is the peak response for each formoterol related compound; and r_s is the sum of the responses for all the peaks.

Content of related compound I *(diastereoisomer)***—**

TEST 1—

Standard solution—Dissolve 10 mg of USP Formoterol Fumarate Resolution Mixture RS in 1 mL of dimethylformamide. Add 100 µL of *N*-(trimethylsilyl)imidazole, and mix.

Test solution—Dissolve 10 mg of Formoterol Fumarate in 1 mL of dimethylformamide. Add 100 µL of *N*-(trimethylsilyl)imidazole, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—The gas chromatograph is equipped with a flame-ionization detector, a 0.32-mm × 30-m fused-silica capillar y column coated with a 0.25-µm film of stationar y phase G27, and a split injection system. The carrier gas is helium, flowing at a rate of about 2 mL per minute and a split ratio of about 75:1. The injection port and the detector temperatures are maintained at about 280° and 300°, respectively. The column temperature is programmed as follows. Initially the column temperature is equilibrated at 220° for 5 minutes, then the temperature is increased at a rate of 1° per minute to 250°, and maintained at 250° for 20 minutes. Chromatograph the *Standard solution,* and record the peak responses as directed for *Procedure:* the resolution, *R,* between formoterol related compound I and formoterol is not less than 1.2.

Procedure—Separately inject equal volumes (about 2 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the peak responses for formoterol related compound I and formoterol. Disregard all other peaks. Calculate the per centage of formoterol related compound I in the portion of Formoterol Fumarate taken by the formula:

$$100(r_i / r_s)$$

in which r_i is the peak response for formoterol related compound I, and r_s is the sum of the responses of both formoterol and formoterol related compound I peaks: not more than 0.3% of formoterol related compound I is found.

TEST 2—

Potassium phosphate solution—Dissolve 5.3 g of tribasic potassium phosphate, trihydrate, in 1000 mL of water, and mix. Adjust the pH with potassium hydroxide or phosphoric acid to 12.0 ± 0.1.

Mobile phase—Prepare a filtered degassed mixture of *Potassium phosphate solution* and acetonitrile (88:12).

Standard solution—Dissolve 5 mg of USP Formoterol Fumarate Resolution Mixture RS in water, dilute with water to 50 mL, and mix.

Test solution—Dissolve 5 mg of Formoterol Fumarate in water, dilute with water to 50 mL, and mix.

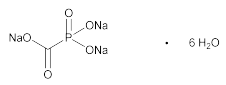
Diluted test solution—Dilute 1 mL of the *Test solution* with water to 20 mL. Dilute 1 mL of this solution with water to 25 mL.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 225-nm detector and a 4.6-mm × 15-cm column that contains packing L67 (see *Chromatographic Reagents* under *Reagents, Indicators, and Solutions*). The flow rate is about 0.5 mL per minute. Chromatograph the *Standard solution,* and record the peak responses as directed for the *Procedure:* the peak-to-valley ratio (H_P / H_V) of formoterol related compound I and formoterol is not less than 2.5, where H_P is the height above the baseline of the peak due to formoterol related compound I, and H_V is the height above the baseline of the lowest point of the cur ve separating this peak from the peak due to formoterol.

Procedure—Separately inject equal volumes (20 µL) of the *Test solution* and the *Diluted test solution* into the chromatograph, record the chromatograms, and measure the peak responses for formoterol and formoterol related compound I. The area due to formoterol related compound I is not more than 1.5 times the area of the principal peak in the chromatogram obtained with the *Diluted test solution:* not more than 0.3% of formoterol related compound I is found.

Assay—Transfer about 350 mg of Formoterol Fumarate, accurately weighed, to a titration vessel, dissolve in 50 mL of anhydrous acetic acid, and titrate with 0.1 M per chloric acid VS, determining the endpoint potentiometrically. Per form a blank determination, and make any necessar y correction. Each mL of 0.1 M perchloric acid is equivalent to 40.24 mg of $(C_{19}H_{24}N_2O_4)_2 \cdot C_4H_4O_4$.

Foscarnet Sodium



$CNa_3O_5P \cdot 6H_2O$ 300.04
Phosphinecarboxylic acid, dihydroxy-, oxide, trisodium salt, hexahydrate.
Phosphonoformic acid, trisodium salt, hexahydrate [34156-56-4].