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Sulfamethoxazole and Trimethoprim Oral Suspension

DEFINITION

Sulfamethoxazole and Trimethoprim Oral Suspension contains NLT 90.0% and NMT 110.0% of the labeled amounts of sulfamethoxazole ($C_{10}H_{11}N_3O_3S$) and trimethoprim ($C_{14}H_{18}N_4O_3$).

IDENTIFICATION

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

ASSAY

• **Procedure**

Mobile phase: Mix 1400 mL of water, 400 mL of acetonitrile, and 2.0 mL of triethylamine in a 2000-mL volumetric flask. Allow to equilibrate to room temperature, and adjust with 0.2 N sodium hydroxide or dilute glacial acetic acid (1 in 100) to a pH of 5.9 ± 0.1. Dilute with water to volume, and pass through a filter of 0.45-µm pore size.

Standard stock solution: 0.32 mg/mL of USP Trimethoprim RS and 0.32*J* mg/mL of USP Sulfamethoxazole RS in methanol, where *J* is the ratio of the labeled amount, in mg, of sulfamethoxazole to the labeled amount, in mg, of trimethoprim in the dosage form

Standard solution: 0.032 mg/mL of USP Trimethoprim RS per mL and 0.032*J* mg/mL of USP Sulfamethoxazole RS per mL in *Mobile phase* from *Standard stock solution*

Sample stock solution: Transfer a volume of Oral Suspension, equivalent to 80 mg of sulfamethoxazole, to a 50-mL volumetric flask with the aid of 30 mL of methanol. Sonicate the mixture for 10 min with occasional shaking. Allow to equilibrate to room temperature, dilute with methanol to volume, and centrifuge. Use the filtrate in the preparation of the *Sample solution*.

Sample solution: Nominally 0.16 mg/mL of sulfamethoxazole in *Mobile phase* from *Sample stock solution*. Filter the solution.

Chromatographic system

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

Mode: LC

Detector: UV 254 nm

Column: 3.9-mm × 30-cm; 10-µm packing L1

Flow rate: 2 mL/min

Injection volume: 20 µL

System suitability

Sample: *Standard solution*

[Note—The relative retention times for trimethoprim and sulfamethoxazole are 1.0 and 1.8, respectively.]

Suitability requirements

Resolution: NLT 5.0 between sulfamethoxazole and trimethoprim

Tailing factor: NMT 2.0 for sulfamethoxazole and trimethoprim

Relative standard deviation: NMT 2.0%

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of trimethoprim ($C_{14}H_{18}N_4O_3$) and sulfamethoxazole ($C_{10}H_{11}N_3O_3S$) in the portion of Oral Suspension taken:

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

r_U = peak response of trimethoprim or sulfamethoxazole from the *Sample solution*

r_S = peak response of trimethoprim or sulfamethoxazole from the *Standard solution*

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

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

Acceptance criteria: 90.0%–110.0% each of sulfamethoxazole ($C_{10}H_{11}N_3O_3S$) and trimethoprim ($C_{14}H_{18}N_4O_3$)

PERFORMANCE TESTS

- **Uniformity of Dosage Units ⟨905⟩:** Meets the requirements for oral suspension packaged in single-unit containers
- **Deliverable Volume ⟨698⟩:** Meets the requirements for oral suspension packaged in multiple-unit containers

IMPURITIES

- **Organic Impurities**

Solution A: Triethylamine and water (2.5:2000). Adjust with glacial acetic acid to a pH of 5.9.

Solution B: Acetonitrile

Mobile phase: See *Table 1*.

Table 1

Time (min)	Solution A (%)	Solution B (%)
0	90	10
10	80	20
25	60	40
30	20	80
31	90	10
35	90	10

Diluent: *Solution A* and *Solution B* (75:25)

System suitability solution: 1 mg/mL of USP Sulfamethoxazole RS; 0.2 mg/mL of USP Trimethoprim RS; 1 µg/mL each of USP Sulfamethoxazole N4-Glucoside RS, USP Sulfamethoxazole Related Compound C RS, and 0.3 µg/mL each of USP Trimethoprim Related Compound A RS, USP Trimethoprim Related Compound B RS, and USP Diaveridine RS in *Diluent*

Standard stock solution A: 0.3 mg/mL of USP Sulfamethoxazole N4-Glucoside RS, and 0.05 mg/mL each of USP Sulfamethoxazole Related Compound C RS and USP Sulfamethoxazole RS in *Diluent*. Sonicate for 5 min to dissolve.

Standard stock solution B: 0.03 mg/mL each of USP Trimethoprim RS, USP Trimethoprim Related Compound A RS, USP Trimethoprim Related Compound B RS, and USP Diaveridine RS in *Diluent*. Sonicate for 5 min to dissolve.

Standard solution: 0.03 mg/mL of USP Sulfamethoxazole N4-Glucoside RS; 5 µg/mL each of USP Sulfamethoxazole Related Compound C RS and USP Sulfamethoxazole RS from *Standard stock solution A*; and 1 µg/mL each of USP Trimethoprim RS, USP Trimethoprim Related Compound A RS, USP Trimethoprim Related Compound B RS, and USP Diaveridine RS from *Standard stock solution B* in *Diluent*

Sample solution: Nominally 1 mg/mL of sulfamethoxazole and 0.2 mg/mL of trimethoprim from a volume of Oral Suspension in *Diluent*. Sonicate for 15 min in *Diluent* before diluting to final volume.

Chromatographic system

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

Mode: LC

Detector: UV 240 nm

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

Flow rate: 0.8 mL/min

Injection volume: 20 µL

System suitability

Sample: *System suitability solution*

Suitability requirements

Resolution: NLT 1.5 between trimethoprim and trimethoprim related compound A; and NLT 1.5 between sulfamethoxazole and trimethoprim related compound B

Relative standard deviation: NMT 2.0% for sulfamethoxazole related compound C, sulfamethoxazole N_4-glucoside, diaveridine, trimethoprim, trimethoprim related compound A, sulfamethoxazole, and trimethoprim related compound B

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of sulfanilic acid and sulfanilamide in the portion of Oral Suspension taken:

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

r_U = peak response of sulfanilic acid or sulfanilamide from the *Sample solution*

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

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

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

F = relative response factor

Calculate the percentage of sulfamethoxazole related compound C and sulfamethoxazole N_4-glucoside in the portion of Oral Suspension taken:

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

r_U = peak response of sulfamethoxazole related compound C or sulfamethoxazole N_4-glucoside from the *Sample solution*

r_S = peak response of sulfamethoxazole related compound C or sulfamethoxazole N_4-glucoside from the *Standard solution*

C_S = concentration of USP Sulfamethoxazole Related Compound C RS or USP Sulfamethoxazole N4-Glucoside RS in the *Standard solution* (mg/mL)

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

Calculate the percentage of diaveridine, trimethoprim related compound A, trimethoprim related compound B, and any other unspecified degradation product in the portion of Oral Suspension taken:

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

r_U = peak response of diaveridine, trimethoprim related compound A, trimethoprim related compound B, or any other unspecified degradation product from the *Sample solution*

r_S = peak response of diaveridine, trimethoprim related compound A, trimethoprim related compound B, or trimethoprim (for any other unspecified degradation product) from the *Standard solution*

C_S = concentration of USP Diaveridine RS, USP Trimethoprim Related Compound A RS, USP Trimethoprim Related Compound B RS, or USP Trimethoprim RS (for any other unspecified degradation product) in the *Standard solution* (mg/mL)

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

Acceptance criteria: See *Table 2*. Disregard limit: 0.01%.

Table 2

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Sulfanilic acid	0.18	2.4	0.3
Sulfanilamide	0.32	1.4	0.5
Sulfamethoxazole related compound C	0.36	—	0.2
Sulfamethoxazole related compound F[a]	0.50	—	—

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Sulfamethoxazole N_4-glucoside	0.54	—	3.0
Diaveridine	0.62	—	0.5
Trimethoprim	0.71	—	—
Trimethoprim related compound A	0.74	—	0.5
Sulfamethoxazole related compound A[a]	0.81	—	—
Sulfamethoxazole	1.00	—	—
Trimethoprim related compound B	1.03	—	0.5
Any other unspecified degradation product	—	—	0.2

[a] Process related impurities monitored in the drug substance.

SPECIFIC TESTS

- **pH** ⟨791⟩**:** 5.0–6.5
- **Alcohol Determination,** *Method II*⟨611⟩**:** NMT 0.5% of alcohol (C_2H_5OH)

ADDITIONAL REQUIREMENTS

- **Packaging and Storage:** Preserve in tight, light-resistant containers. Store at controlled room temperature. Protect from light.
- **USP Reference Standards** ⟨11⟩

USP Alcohol Determination–Acetonitrile RS
USP Alcohol Determination–Alcohol RS
USP Diaveridine RS
5-(3,4-Dimethoxybenzyl)pyrimidine-2,4-diamine.
$C_{13}H_{16}N_4O_2$ 260.29
USP Sulfamethoxazole RS
USP Sulfamethoxazole N4-Glucoside RS
4-(Beta-D-glucopyranosylamino)-*N*-(5-methyl-3-isoxazolyl)-benzenesulfonamide.
$C_{16}H_{21}N_3O_8S$ 415.42
USP Sulfamethoxazole Related Compound C RS
5-Methyl-3-isoxamine.
$C_4H_6N_2O$ 98.10
USP Trimethoprim RS
USP Trimethoprim Related Compound A RS
4-Amino-5-(3,4,5-trimethoxybenzyl)pyrimidin-2-ol.
$C_{14}H_{17}N_3O_4$ 291.30
USP Trimethoprim Related Compound B RS
(2,4-Diaminopyrimidin-5-yl)(3,4,5-trimethoxyphenyl)methanone.
$C_{14}H_{16}N_4O_4$ 304.30

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

Topic/Question	Contact	Expert Committee
SULFAMETHOXAZOLE AND TRIMETHOPRIM ORAL SUSPENSION	Documentary Standards Support	SM12020 Small Molecules 1

Topic/Question	Contact	Expert Committee
REFERENCE STANDARD SUPPORT	RS Technical Services RSTECH@usp.org	SM12020 Small Molecules 1

Chromatographic Database Information: Chromatographic Database

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