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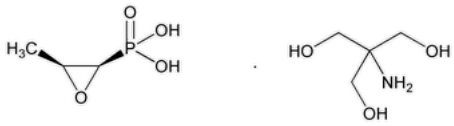
# Fosfomycin Tromethamine



$C_3H_7O_4P \cdot C_4H_{11}NO_3$ 259.19

Phosphonic acid, (3-methyloxiranyl)-, (2*R*-cis)-, compd. with 2-amino-2-(hydroxymethyl)-1,3-propanediol (1:1); (1*R*,2*S*)-(1,2-Epoxypropyl)phosphonic acid, compound with 2-amino-2-(hydroxymethyl)-1,3-propanediol (1:1) CAS RN®: 78964-85-9; UNII: 7FXW6U30GY.

***Change to read:***

**DEFINITION**

Fosfomycin Tromethamine contains NLT 98.0% and NMT 102.0% of ▲fosfomycin tromethamine▲ (IRA 1-Mar-2024) ($C_3H_7O_4P \cdot C_4H_{11}NO_3$), calculated on the anhydrous basis.

**IDENTIFICATION**

- **A.** **Spectroscopic Identification Tests ⟨197⟩, *Infrared Spectroscopy*:** 197K
- **B.** The retention time of the fosfomycin peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay*.
- **C.** The retention time of the tromethamine peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay*.

**ASSAY**

***Change to read:***

- **Procedure**

[Note—Prepare the solutions immediately before use.]

**Mobile phase:** 10.89 g/L of monobasic potassium phosphate in water

**Solution A:** ▲15 mg/mL of Fosfomycin Tromethamine prepared as follows.▲ (IRA 1-Mar-2024) Wet 300 mg of ▲Fosfomycin Tromethamine▲ (IRA 1-Mar-2024) with 60 µL of water, and heat in an oven at 60° for 24 h. Dissolve the residue, and dilute with *Mobile phase* to 20.0 mL.

**System suitability solution:** ▲120 mg/mL of Fosfomycin Tromethamine in *Solution A*▲ (IRA 1-Mar-2024)

**Standard solution:** 120 mg/mL of USP Fosfomycin Tromethamine RS in *Mobile phase*

**Sample solution:** 120 mg/mL of Fosfomycin Tromethamine in *Mobile phase*

**Chromatographic system**

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

**Mode:** LC

**Detector:** Differential refractometer

**Column:** 4.6-mm × 25-cm; 5-µm packing L8

**Detector temperature:** 35°

**Flow rate:** 1 mL/min

**Injection volume:** 5 µL

**Run time:** ▲NLT 2 times▲ (IRA 1-Mar-2024) the retention time of fosfomycin

**System suitability**

**Sample:** *System suitability solution*

▲[Note—See *Table 1* for the relative retention times of fosfomycin tromethamine adduct, tromethamine phosphate, fosfomycin open ring, and fosfomycin.]▲ (IRA 1-Mar-2024)

**Suitability requirements**

**Peak-to-valley ratio:** NLT 1.5.▲Ratio is based on the height above the baseline due to the tromethamine phosphate peak and to the height above the baseline of the lowest point of the curve separating this peak from the peak due to the fosfomycin tromethamine adduct.▲ (IRA 1-Mar-2024)

**Resolution:** NLT 1.5 between fosfomycin open ring and fosfomycin

**Analysis**

**Samples:** *Standard solution* and *Sample solution*

Calculate the percentage of ▲fosfomycin tromethamine▲ (IRA 1-Mar-2024) ($C_3H_7O_4P \cdot C_4H_{11}NO_3$) in the portion of Fosfomycin Tromethamine taken:

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

$r_U$ = peak response of fosfomycin from the *Sample solution*

$r_S$ = peak response of fosfomycin from the *Standard solution*

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

$C_U$ = concentration of Fosfomycin Tromethamine in the *Sample solution* (mg/mL)

**Acceptance criteria:** 98.0%–102.0% on the anhydrous basis

## IMPURITIES

***Change to read:***

▲▲ (IRA 1-Mar-2024)

• **Limit of Inorganic Phosphates**

**Solution A:** Dissolve 4 g of finely powdered ammonium molybdate and 0.1 g of finely powdered ammonium vanadate in 70 mL of water. Add 20 mL of nitric acid, and dilute with water to 100 mL.

**Standard solution:** Dissolve 7.16 mg of monobasic potassium phosphate in 1000 mL of water (5 ppm $PO_4$). [Note—Prepare immediately before use.]

**Sample solution:** Dissolve 0.1 g of Fosfomycin Tromethamine in 3 mL of 2 N nitric acid, and dilute with water to 10 mL.

**Analysis:** In separate containers, transfer 5 mL of the *Standard solution* and 5 mL of the *Sample solution*. Add 5 mL of water and 5 mL of *Solution A* to both solutions, and shake vigorously. After 5 min, any color in the *Sample solution* is not more intense than the *Standard solution*.

**Acceptance criteria:** NMT 500 ppm

***Change to read:***

• **Organic Impurities**

[Note—Prepare the solutions immediately before use.]

**Mobile phase, Sample solution, Solution A,** and **System suitability solution**▲▲ (IRA 1-Mar-2024)**:** Prepare as directed in the *Assay*.

**Standard solution:** 0.36 mg/mL of USP Fosfomycin Tromethamine RS in *Mobile phase*

**Chromatographic system**

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

**Mode:** LC

**Detector:** Differential refractometer

**Column:** 4.6-mm × 25-cm; 5-µm packing L8

**Detector temperature:** 35°

**Flow rate:** 1 mL/min

**Injection volume:** 10 µL

**Run time:** ▲NLT 2 times▲ (IRA 1-Mar-2024) the retention time of fosfomycin

▲**System suitability**

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

[Note—The relative retention times in *Table 1* are provided as information that could aid in peak assignment.]

**Table 1**

| Name | Relative Retention Time |
|---|---|
| Tromethamine[a] | 0.30 |
| Fosfomycin tromethamine adduct[b] | 0.48 |
| Tromethamine phosphate[c] | 0.54 |
| Fosfomycin open ring[d] | 0.88 |

| Name | Relative Retention Time |
|---|---|
| Fosfomycin | 1.00 |
| Fosfomycin dimer tromethamine adduct[e] | 1.27 |

[a] Salt counter ion; two peaks will appear due to tromethamine; 2-Amino-2-(hydroxymethyl)-1,3-propanediol.

[b] 2-[2-Amino-3-hydroxy-2-(hydroxymethyl)propoxy]-1-hydroxypropylphosphonic acid.

[c] 2-Amino-3-hydroxy-2-(hydroxymethyl)propyl dihydrogen phosphate.

[d] (1,2-Dihydroxypropyl)phosphonic acid.

[e] 2-({2-[2-Amino-3-hydroxy-2-(hydroxymethyl)propoxy]-1-hydroxypropyl} hydroxyphosphoryloxy)-1-hydroxypropylphosphonic acid.

**Suitability requirements**

**Peak-to-valley ratio:** NLT 1.5, *System suitability solution*. Ratio is based on the height above the baseline due to the tromethamine phosphate peak and to the height above the baseline of the lowest point of the curve separating this peak from the peak due to the fosfomycin tromethamine adduct.

**Resolution:** NLT 1.5 between fosfomycin open ring and fosfomycin, *System suitability solution*

**Relative standard deviation:** NMT 10.0%, *Standard solution* ▲(IRA 1-Mar-2024)

**Analysis**

**Samples:** *Standard solution* and *Sample solution*

Calculate the percentage of ▲each impurity▲(IRA 1-Mar-2024) in the portion of Fosfomycin Tromethamine taken:

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

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

$r_S$ = peak response of fosfomycin from the *Standard solution*

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

$C_U$ = concentration of Fosfomycin Tromethamine in the *Sample solution* (mg/mL)

▲(IRA 1-Mar-2024)

**Acceptance criteria:**

▲See *Table 2*. The reporting threshold is 0.05%.

**Table 2**▲(IRA 1-Mar-2024)

| Name | Acceptance Criteria, NMT (%) |
|---|---|
| Fosfomycin tromethamine adduct | 0.3 |
| Tromethamine phosphate | 0.1 |
| Fosfomycin open ring | 0.3 |
| Fosfomycin dimer tromethamine adduct | 0.1 |
| Any ▲unspecified▲(IRA 1-Mar-2024) impurity | 0.1 |
| Total impurities | 0.5 |

**SPECIFIC TESTS**

***Change to read:***

• **pH** ⟨791⟩

▲**Sample solution:** 50 mg/mL solution of Fosfomycin Tromethamine in carbon dioxide-free water

**Acceptance criteria:** 3.5–5.5▲(IRA 1-Mar-2024)

***Change to read:***

- **Optical Rotation** ⟨781S⟩, *Procedures, Specific Rotation*

  **Sample solution:** 50 mg/mL ▲of Fosfomycin Tromethamine▲ (IRA 1-Mar-2024) in carbon dioxide-free water

  **Detection:** Mercury lamp at 365 nm

  **Acceptance criteria:** −13.5° to −12.5°

- **Water Determination** ⟨921⟩, *Method I*, *Method Ic*: NMT 0.5%

## ADDITIONAL REQUIREMENTS

- **Packaging and Storage:** Preserve in tight containers. Store at controlled room temperature.
- **USP Reference Standards** ⟨11⟩
  USP Fosfomycin Tromethamine RS

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

| Topic/Question | Contact | Expert Committee |
|---|---|---|
| FOSFOMYCIN TROMETHAMINE | Documentary Standards Support | SM12020 Small Molecules 1 |

**Chromatographic Database Information:** Chromatographic Database

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