Fosfomycin sodium

Photograph (macro) of the substance

01/2005:1329

**FOSFOMYCIN SODIUM**

Fosfomycinum natricum

![Chemical Structure](image)

**DEFINITION**

Fosfomycin sodium contains not less than 95.0 per cent and not more than the equivalent of 101.0 per cent of disodium (2R,3S)-(3-methyloxiran-2-yl)phosphonate, calculated with reference to the anhydrous substance.

**CHARACTERS**

A white or almost white, very hygroscopic powder, very soluble in water, sparingly soluble in methanol, practically insoluble in ethanolic in and in methylene chloride.

**IDENTIFICATION**

First identification: A, D.
Second identification: B, C, D.

A. Examine by infrared absorption spectrophotometry (2.2.24), comparing with the Ph. Eur. reference spectrum of fosfomycin sodium. Examine the substance as discs prepared using potassium bromide.

B. Dissolve about 0.1 g in 3 ml of a 25 per cent V/V solution of perchloric acid R. Add 1 ml of 0.1 M sodium periodate and heat on a water-bath for 30 min. Allow to cool and add 50 ml of water R. Neutralise with a saturated solution of sodium hydrogen carbonate R and add 1 ml of a freshly prepared 400 g/l solution of potassium iodide R. Prepare a blank at the same time and in the same manner. The test solution remains colourless and the blank is orange.

C. To about 8 mg of the substance to be examined, add 2 ml of water R, 1 ml of perchloric acid R and 2 ml of 0.1 M sodium periodate. Heat on a water-bath for 10 min and add, without cooling, 1 ml of ammonium molybdate solution R5 and 1 ml of aminoxyphosphonic acid solution R. Allow to stand for 30 min. A blue colour develops.

D. It gives reaction (a) of sodium (2.3.1).

**TESTS**

**Solution S.** Dissolve 5.0 g in carbon dioxide-free water R and dilute to 50.0 ml with the same solvent.

**Appearance of solution.** Solution S is clear (2.2.1) and not more intensely coloured than reference solution B9 (2.2.2, Method II). *pH* (2.2.3). Dilute 10 ml of solution S to 20 ml with carbon dioxide-free water R. The *pH* of the solution is 9.0 to 10.5.

**Specific optical rotation** (2.2.7). Dissolve 2.5 g in water R and dilute to 50.0 ml with the same solvent. Measured at 405 nm using a mercury lamp, the specific optical rotation is −13.0 to −15.0, calculated with reference to the anhydrous substance.

**Disodium 1,2-(dihydroxypropyl)phosphonate.** Not more than 1.0 per cent. Into a glass-stoppered flask, dissolve 0.200 g of the substance to be examined in 100.0 ml of water R. Add 50 ml of 0.5 M phthalate buffer solution *pH* 6.4 R and 5.0 ml of 0.005 M sodium periodate, close and shake. Allow to stand protected from light for 90 min. Add 10 ml of a freshly prepared 400 g/l solution of potassium iodide R, close and shake for 2 min. Titrate with 0.0025 M sodium arsenite until the yellow colour almost disappears. Add 2 ml of starch solution R and titrate slowly until the colour is completely discharged. Carry out a blank test under the same conditions. Calculate the percentage content of C,H,CaO,P from the expression:

\[
\frac{(n_1 - n_2) \times c \times 100}{m(100 - H)} \times 100
\]

**ASSAY**

Into a glass-stoppered flask, dissolve 0.120 g of the substance to be examined in 20.0 ml of 0.1 M sodium periodate. Add 5 ml of 50 per cent V/V solution of perchloric acid R and shake. Heat on a water-bath at 37 °C for 105 min. Add 50 ml of water R and immediately adjust to *pH* 6.4 with a saturated solution of potassium hydrogen carbonate R and dilute to 50.0 ml with the same solvent.

**Heavy metals** (2.4.8). 12 ml of solution S complies with limit test A for heavy metals (20 ppm). Prepare the standard using lead standard solution (2 ppm Pb) R.

**Water** (2.5.12). Not more than 1.0 per cent, determined on 0.50 g by the semi-micro determination of water. Use as the solvent a mixture of 1 volume of pyridine R and 3 volumes of ethylene glycol R.

**Bacterial endotoxins** (2.6.14): less than 0.083 IU/mg, if intended for use in the manufacture of parenteral dosage forms without a further appropriate procedure for removal of bacterial endotoxins.

**STORAGE**

Store in an airtight container, protected from light.

**IMPURITIES**

A. calcium (1,2-dihydroxypropyl)phosphonate.
solution of sodium hydrogen carbonate R. Add 10 ml of a freshly prepared 400 g/l solution of potassium iodide R, close and allow to stand for 2 min. Titrate with 0.1 M sodium arsenite until the yellow colour almost disappears. Add 2 ml of starch solution R and titrate slowly until the colour is completely discharged. Carry out a blank test under the same conditions.

Calculate the percentage content of C₇H₁₈NO₇P from the expression:

\[
\frac{(n_1 - n_2) \times c \times 91 \times 100}{m(100 - H)} \times 100 - G
\]

where:
- \(m\) = quantity of the substance to be examined, in milligrams,
- \(n_1\) = volume of 0.1 M sodium arsenite used in the titration of the test solution,
- \(n_2\) = volume of 0.1 M sodium arsenite used in the blank titration,
- \(c\) = molarity of the sodium arsenite solution,
- \(G\) = percentage content of disodium 1,2-(dihydroxypropyl)phosphonate,
- \(H\) = percentage content of water.

STORAGE
Store in an airtight container, protected from light. If the substance is sterile, store in a sterile, airtight, tamper-proof container.

LABELLING
The label states, where applicable, that the substance is free from bacterial endotoxins.

IMPURITIES

A. disodium (1,2-dihydroxypropyl)phosphonate.

01/2005:1425

FOSFOMYCIN TROMETAMOL

Fosfomycinum trometamolum

C₇H₁₈NO₇P  \(M_r\) 259.2

DEFINITION
Fosfomycin trometamol contains not less than 98.0 per cent and not more than the equivalent of 102.0 per cent of 1,3-dihydroxy-2-(hydroxymethyl)propan-2-aminium (2R,3S)-(3-methyloxiran-2-yl)phosphonate, calculated with reference to the anhydrous substance.

CHARACTERS
A white or almost white powder, hygroscopic, very soluble in water, slightly soluble in alcohol and in methanol, practically insoluble in acetone.

IDENTIFICATION
First identification: A.
Second identification: B. C.

A. Examine by infrared absorption spectrophotometry (2.2.24), comparing with the spectrum obtained with fosfomycin trometamol CRS.

B. Examine by thin-layer chromatography (2.2.27), using cellulose for chromatography R as the coating substance. Test solution. Dissolve 50 mg of the substance to be examined in water R and dilute to 10 ml with the same solvent.

Reference solution. Dissolve 50 mg of fosfomycin trometamol CRS in water R and dilute to 10 ml with the same solvent.

C. To about 15 mg of the substance to be examined, add 2 ml of water R, 1 ml of perchloric acid R and 2 ml of 0.1 M sodium periodate. Heat on a water-bath for 10 min and add, without cooling, 1 ml of ammonium molybdate solution R5 and 1 ml of aminohydroxynaphthalenesulphonic acid solution R. Allow to stand for 30 min. A blue colour develops.

TESTS

Solution S. Dissolve 1.00 g in carbon dioxide-free water R and dilute to 20.0 ml with the same solvent.

pH (2.2.3). The pH of solution S is 3.5 to 5.5.

Specific optical rotation (2.2.7). Measured at 365 nm using a mercury lamp, the specific optical rotation is \(-13.5\) to \(-12.5\), determined on solution S and calculated with reference to the anhydrous substance.

Related substances. Examine by liquid chromatography (2.2.29) as prescribed under Assay. Inject 5 µl of the test solution, 5 µl of reference solution (b) and 5 µl of the blank solution. Continue the chromatography for twice the retention time of the peak due to fosfomycin. In the chromatogram obtained with the test solution: the area of any peak corresponding to impurity A is not greater than the area of the corresponding peak in the chromatogram obtained with reference solution (b) (0.5 per cent, calculated as trometamol salts); the area of any peak, apart from the principal peak, two peaks corresponding to trometamol and any peak corresponding to impurity A, is not greater than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.5 per cent, calculated as trometamol salts). The sum of the areas of all the peaks, apart from the principal peak and the two peaks corresponding to trometamol, is not greater than twice the area of the principal peak in the chromatogram obtained with reference solution (b) (1 per cent, calculated as trometamol salts). Disregard any peak due to the blank and any peak with an area less than 0.1 times the area of the principal peak in the chromatogram obtained with reference solution (b).

Phosphates. Dissolve 0.1 g in 3 ml of dilute nitric acid R and dilute to 10 ml with water R. To 5 ml of this test solution add 5 ml of water R and 5 ml of molybdovanadic reagent R. Shake vigorously. After 5 min, any colour in the test solution