## Sulfamethoxazole and trimethoprim tablets (Sulfamethoxazoli et trimethoprimi compressi)

Category. Antibacterials.

Storage. Sulfamethoxazole and trimethoprim tablets should be kept in a well-closed container, protected from light.

Additional information. Strengths in the current WHO Model list of essential medicines:

100 mg Sulfamethoxazole, 20 mg Trimethoprim

400 mg Sulfamethoxazole, 80 mg Trimethoprim

800 mg Sulfamethoxazole, 160 mg Trimethoprim

Strengths in the WHO Model list of essential medicines for children:

100 mg Sulfamethoxazole, 20 mg Trimethoprim

400 mg Sulfamethoxazole, 80 mg Trimethoprim

Requirements

Comply with the monograph for <u>*Tablets*</u>.

**Definition.** Sulfamethoxazole and trimethoprim tablets contain Sulfamethoxazole and Trimethoprim. They contain not less than 90.0% and not more than 110.0% of the amounts of Sulfamethoxazole ( $C_{10}H_{11}N_3O_3S$ ) and Trimethoprim ( $C_{14}H_{18}N_4O_3$ ) stated on the label.

## **Identity tests**

A. Carry out test A.1 or, where UV detection is not available, test A.2.

A.1 Carry out the test as described under <u>1.14.1 Chromatography</u>, Thin-layer chromatography using silica gel R6 as the coating substance and a mixture of 100 volumes of dicloromethane R, 10 volumes of methanol R, 5 volumes of dimethylformamide R as the mobile phase. Apply separately to the plate 5  $\mu$ l of each of the following two solutions in methanol R. For solution (A) add 20 mL to a quantity of the powdered tablets containing about 400 mg of Sulfamethoxazole, warm for several minutes on a water-bath with frequent shaking, cool and filter. For solution (B) use 20 mg of sulfamethoxazole RS and 4 mg of trimethoprim RS per mL. After removing the plate from the chromatographic chamber allow it to dry exhaustively in air or in a current of cool air. Examine the chromatogram in ultraviolet light (254 nm).

The principal spots obtained with solution (A) correspond in position, appearance and intensity to those obtained with solution (B).

A.2 Carry out the test as described under <u>1.14.1 Chromatography</u>, <u>Thin-layer chromatography</u> using silica gel R5 as the coating substance and the conditions described above under test A.1. Spray the plate with dilute potassium iodobismuthate solution TS.

The principal spots obtained with solution (A) correspond in position, appearance and intensity to those obtained with solution (B).

B. See the test described under "Assay", Method A. The retention times of the principal peaks in the chromatogram obtained with solution (1) are similar to those in the chromatogram obtained with solution (2).

## Dissolution

Carry out the test as described under <u>5.5 Dissolution test for solid oral dosage forms</u> using as the dissolution medium 900 mL of hydrochloric acid (~3.6 g/l) TS and rotating the paddle at 75 revolutions per minute. At 30 minutes withdraw a sample of about 10 mL of the medium through an in-line filter. Make any necessary volumetric adjustment if needed to obtain concentrations comparable to the solution (4) (solution (3)). For standard solution use 0.22 mg of trimethoprim RS and 1.11 mg of sulfamethoxazole RS per mL of methanol R. Dilute 5.0 mL of this solution to 50.0 mL with hydrochloric acid (~3.6 g/l) TS (solution (4)). Determine the content of Sulfamethoxazole ( $C_{10}H_{11}N_3O_3S$ ) and Trimethoprim ( $C_{14}H_{18}N_4O_3$ ) as described under "Assay", Method A, using solution (3) and solution (4) in place of solution (1) and solution (2), respectively.

For each of the six tablets tested calculate the total amount of sulfamethoxazole ( $C_{10}H_{11}N_3O_3S$ ) and trimethoprim ( $C_{14}H_{18}N_4O_3$ ) in the medium from the results obtained. For both substances the amount in the solution for each tablet is not less than 75% of the amount stated on the label. For either substance, if the amount obtained for one of the six tablets is less than 75%, repeat the test using a further six tablets; the average amount for all 12 tablets tested is not less than 70% and no tablet releases less than 55%.

## Assay

-Either method A or methods B and C may be applied.

A. Carry out the test as described under <u>1.14.1 Chromatography</u>, High-performance liquid chromatography using a stainless steel column (25 cm x 4.6 mm) packed with particles of base-deactivated silica gel, the surface of which has been modified with chemically-bonded octadecylsilyl groups (5  $\mu$ m). As the mobile phase use a solution prepared as follows: mix 1400 mL of water R, 400 mL of acetonitrile R and 2.0 mL of triethylamine R in a 2000 mL volumetric flask. Allow to equilibrate to room temperature and adjust with dilute glacial acetic acid (~10 g/l) TS to pH 5.9. Dilute to volume with water R and filter.

Prepare the following solutions. For solution (1) weigh and powder 20 tablets, transfer a quantity of the powder containing about 160 mg of Sulfamethoxazole, accurately weighed, into a 100 mL volumetric flask. Add about 50 mL of methanol R and sonicate, with intermittent shaking, for 5 minutes. Allow to cool to room temperature, make up to volume with methanol R, mix and filter. Dilute 5.0 mL of the filtrate to 50.0 mL with the mobile phase. For solution (2) use 0.32 mg of trimethoprim RS and 1.60 mg of sulfamethoxazole RS per mL of methanol R. Dilute 5.0 mL of this solution to 50.0 mL with the mobile phase.

Operate with a flow rate of 1.0 mL per minute. As a detector use an ultraviolet spectrophotometer set at a wavelength of 254 nm.

Inject separately  $30 \ \mu$ l each of solutions (1) and (2) and record the chromatogram for 1.5 times the retention time of sulfamethoxazole. In the chromatogram obtained with solution (2) the two principal peaks elute in the order: trimethoprim (retention time about 6 minutes); sulfamethoxazole (retention time about 11 minutes). The test is not valid unless the resolution factor between the peaks due to sulfamethoxazole and to trimethoprim is at least 5.0.

Measure the areas of the peak responses obtained in the chromatograms from solutions (1) and (2) and calculate the content of sulfamethoxazole ( $C_{10}H_{11}N_3O_3S$ ) and trimethoprim ( $C_{14}H_{18}N_4O_3$ ) in the tablets.

B. Weigh and powder 20 tablets. To a quantity of the powder containing 50 mg of Trimethoprim add 30 mL of sodium hydroxide (~4 g/l) TS and extract with four quantities of 50 mL of dichloromethane R, washing each extract twice with a quantity of 10 mL of sodium hydroxide (~4 g/l) TS. Combine the dichloromethane extracts and extract with four quantities of 50 mL of acetic acid (~60 g/l) TS. Wash the combined aqueous extracts with 5 mL of dichloromethane R and dilute to 250.0 mL with acetic acid (~60 g/l). To 10 mL of this solution add 10 mL of acetic acid (~60 g/l) and dilute to 100.0 mL with water R. Measure the absorbance of the resulting solution at the maximum at 271 nm. Calculate the amount of trimethoprim (C<sub>14</sub>H<sub>18</sub> N<sub>4</sub>O<sub>3</sub>) using an absorptivity value of 20.4 ( $A_{1m}^{1m} = 204$ ).

C. Weigh and powder 20 tablets. Dissolve a quantity of the powder containing 500 mg of Sulfamethoxazole, accurately weighed, in 60 mL of water R and 10 mL of hydrochloric acid (~420 g/l) TS. Add 3 g of potassium bromide R, cool in ice and titrate slowly with sodium nitrite (0.1 mol/l) VS, stirring constantly and determining the end-point potentiometrically.

Each mL of sodium nitrite (0.1 mol/l) VS is equivalent to 25.33 mg of sulfamethoxazole (C<sub>10</sub>H<sub>11</sub>N<sub>3</sub>O<sub>3</sub>S).