



SULFAMETHOXAZOLE AND TRIMETHOPRIM TABLETS

Draft proposal for *The International Pharmacopoeia*

(September 2010)

REVISED DRAFT FOR COMMENT

This document was provided by a quality control expert and was discussed at the recent WHO consultation on specifications for medicines and quality control laboratory issues. Previous comments received have been incorporated into this revised draft. Should you have any comments, please send these to Dr S. Kopp, Manager, Medicines Quality Assurance Programme, Quality Assurance and Safety: Medicines, World Health Organization, 1211 Geneva 27, Switzerland; fax: (+41 22) 791 4730 or e-mails: kopps@who.int with a copy to Ms C. Mendy mendyc@who.int by 3 November 2010.

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Please send any request for permission to:

Dr Sabine Kopp, Quality Assurance Programme, Medicines Quality Assurance Programme, Quality & Safety: Medicines (QSM), Department of Essential Medicines and Pharmaceutical Policies (EMP), World Health Organization, CH-1211 Geneva 27, Switzerland. Fax: (41-22) 791 4730; e-mail: kopps@who.int.

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SCHEDULE FOR THE ADOPTION PROCESS OF DOCUMENT QAS/10.347
International Pharmacopoeia monograph on Sulfamethoxazole and Trimethoprim tablets

	Date
Preparation of first draft by laboratory	February 2010
Preliminary discussion of the first draft during the tele-video-conference on specifications for medicines and quality control laboratory issues	4 March 2010
Discussion of the draft proposal in the consultation on specifications for medicines and quality control laboratory issues	10-12 May 2010
Mailing of revised draft monograph for comments	July 2010
Collation of comments received	August 2010
Revised draft discussed during video-/teleconference on specifications for medicines	25 August 2010
Revised draft mailed out for comments	October 2010
Presentation to WHO Expert Committee on Specifications for Pharmaceutical Preparations	18-22 October 2010
Any further action as required	...

[Note from the Secretariat:

This draft text is proposed for inclusion in The International Pharmacopoeia (Ph.Int.) in the context of a collaboration between the WHO and the Medicines and Healthcare products Regulatory Agency of the United Kingdom of Great Britain and Northern Ireland (MHRA) hosting The British Pharmacopoeia, on which this text is based.]

SULFAMETHOXAZOLE AND TRIMETHOPRIM TABLETS

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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

Requirements

Comply with the monograph for “Tablets”.

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 (C₁₀H₁₁N₃O₃S) and Trimethoprim (C₁₄H₁₈N₄O₃) stated on the label.

[Note from the Secretariat: wider limits than those stated in the BP monograph (92.5%–107.5%) are proposed, to be in line with the policy and limits applied for similar dosage forms in the Ph.Int.]

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 1.14.1. Thin-layer chromatography, using silica gel R6 as the coating substance and a mixture of 100 volumes of dichloromethane R, 10 volumes of methanol R, 5 volumes of dimethylformamide R as the mobile phase. Apply separately to the plate 5 µl 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. 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 1.14.1 Thin-layer chromatography, 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 the test solution are similar to those in the chromatogram obtained with the reference solution.

Dissolution

Carry out the test as described under 5.5 Dissolution test for solid oral dosage forms, 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).

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 contains less than 55%.

[Note from the Secretariat: Two dissolution methods were initially proposed for, respectively, the 20/100 mg and 80/400 mg tablets. A combined procedure, which is applicable to both strengths, is now described.]

Assay

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

- A. Carry out the test as described under 1.14.4 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 μm)¹. 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 through a 0.45- μm membrane.

¹ Hypersil BDS C18 has been found suitable.

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 µl 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 not less than 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 (~4g/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 sufficient water R to produce 100 ml and measure the absorbance of the resulting solution at the maximum at 271 nm. Calculate the amount of Trimethoprim ($C_{14}H_{18}N_4O_3$) using an absorptivity value of 20.4 ($A_{1\%}^{1\text{cm}} = 204$).
- 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 $C_{10}H_{11}N_3O_3S$.

Uniformity of content. Tablets containing 20 mg of Trimethoprim and 100 mg of Sulfamethoxazole comply with the test for 5.1 Uniformity of content for single-dose preparations using Assay Method A.

[Note from Secretariat:

It is intended to revise the general method 5.1 Uniformity of content for single-dose preparations, so it will include the following requirement as stated in the WHO guidelines for registration of fixed-dose combination medicinal products (WHO TRS 929, Annex 5):

- "For solid dosage forms a test and limit for content uniformity should be applied to any active that is present at a weight inferior or equal to 25 mg or when the API comprises 25% or less of a dosage

unit [...] Typically, when any one API is present at less than 25 mg or less than 25% of the weight of a dosage unit, all of the actives are subjected to content uniformity testing."

In 100 mg Sulfamethoxazole and 20 mg Trimethoprim tablets, the test for uniformity of content is therefore applicable to Trimethoprim and to Sulfamethoxazole, using the Assay method described in the monograph, that needs to be adapted in order to measure the content for individual tablets.]

Revised draft for comment