World Health Organization

AMINOSALICYLATE SODIUM DELAYED-RELEASE TABLETS

(AMINOSALICYLATI NATRII COMPRESSI AD TARDATAM LIBERATIONEM)

Draft proposal for inclusion for *The International Pharmacopoeia*

(15 November 2024)

DRAFT FOR COMMENTS

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For any technical queries, please contact **Dr Herbert Schmidt**, Technical Officer, Norms and Standards for Pharmaceuticals, Technical Standards and Specifications (schmidth@who.int), with a copy to Ms Sinéad Jones (jonessi@who.int, nsp@who.int).
Comments should be submitted through the online platform on or by **15 January 2025**. Please note that only comments received by this deadline will be considered for the preparation of this document.
Our working documents are sent out electronically and uploaded into PleaseReview™. The working documents are also placed on the WHO Medicines website (https://www.who.int/teams/health-product-and-policy-standards/standards-and-specifications/pharmaceuticals/working-documents-public-consultation) under the "Working documents in public consultation". If you wish to receive all our draft guidelines during the course of the year, please send your full name, organization/ affiliation, and email address to jonessi@who.int, nsp@who.intand your name will be added to our electronic mailing list and review platform.

SCHEDULE FOR THE ADOPTION PROCESS OF DOCUMENT QAS/20.845:

AMINOSALICYLATE SODIUM DELAYED-RELEASE TABLETS

(AMINOSALICYLATI NATRII COMPRESSI CUM LIBERATIONE PROLONGATA)

Description	Date
Draft monograph received from Collaborating Centre.	March 2020
Discussion at the consultation on Screening Technologies, Laboratory Tools and Pharmacopoeial Specifications for Medicines.	May 2020
Discussion at the consultation on Quality Control and Pharmacopoeial Specifications of Medicines	April 2023
Draft monograph sent out for public consultation.	December 2024 – January 2025
Presentation to the 59th WHO Expert Committee on Specifications for Pharmaceutical Preparations.	October 2025
Further follow-up action as required.	

AMINOSALICYLATE SODIUM DELAYED-RELEASE TABLETS

(AMINOSALICYLATI NATRII COMPRESSI AD TARDATAM LIBERATIONEM)

Category. Antituberculosis.

Storage. Aminosalicylate sodium delayed-release tablets should be kept in a tightly closed container, protected from light.

Additional information. Strength of Aminosalicylic sodium delayed-release tablets available 500 mg per tablets.

Requirements

Comply with the monograph on *Tablets*.

Definition. Aminosalicylate sodium delayed-release tablets contain Aminosalicylate sodium dihydrate. They contain not less than 90.0% and not more than 110.0% of the amount of Aminosalicylate sodium dihydrate ($C_7H_6NNaO_3 \cdot 2H_2O$) stated on the label.

Identity tests

- Any two of tests A, B or C may be applied.

A. Carry out the test as described under *1.14.1 Chromatography,* High-performance liquid chromatography, using the conditions given under "Assay". The retention time of the principal peak in the chromatogram obtained with solution (1) corresponds to the retention time and the UV spectrum of the peak due to aminosalicylate in the chromatogram obtained with solution (2).

D. Carry out as described under *1.6 Spectrophotometry in the visible and ultraviolet regions*. Powder 10 tablets and transfer a quantity of the powder tablets, nominally containing 250 mg of Aminosalicylate sodium dihydrate to a 500 mL volumetric flask, add 3 mL of sodium hydroxide (~40 g/L) TS to

dissolve the substance and dilute with water R to volume. Transfer 5 mL of this solution to a 250 volumetric flask, add 12.5 mL of phosphate buffer, pH 7.0 (0.05 mol/L) TS and dilute with water R to volume. The absorption spectrum of the solution, when observed between 200 nm and 400 nm, exhibits maxima at about 265 and 299 nm.

Alternatively, in combination with identity test A, where a diode array detector is available, record the UV spectra of the principal peaks in the chromatograms with a diode array detector in the range of 220 nm to 400 nm. The UV spectrum of the principal peak in the chromatogram obtained with solution (A) corresponds to the UV spectrum of the peak due to aminosalicylate in the chromatogram obtained with solution (B).

C. Carry out the test as described under *1.14.1 Chromatography,* Thin-layer chromatography, using silica gel R6 as the coating substance and a mixture of 50 volume of ethyl acetate R, 1 volume of ethanol absolute R and 1 volume of anhydrous formic acid R as the mobile phase. Apply separately to the plate 5 µl of each of the following two solutions. For solution (A), shake a quantity of the powdered tablets, nominally containing 20 mg of Aminosalicylate sodium dihydrate, with 10 mL of ethanol (~750 g/L) TS, filter and use the clear filtrate. For solution (B), use a solution containing 2 mg of aminosalicylate sodium RS per mL of ethanol (~750 g/L) TS. After removing the plate from the chromatographic chamber, allow it to dry in air. Examine the chromatogram in ultraviolet light (254 nm).

The principal spot obtained with solution (A) corresponds in position, appearance and intensity to that obtained with solution (B).

Dissolution. Carry out the test as described under *5.5 Dissolution test for solid oral dosage forms* using as the dissolution medium for the acid stage 900 mL of hydrochloric acid (~3.65 g/L) TS. Rotate the basket at 100 revolutions per minute. After 120 minutes, withdraw a sample of 10 mL of the medium through an in-line

filter. Dilute 1.0 mL of this solution to 10.0 mL with phosphate buffer pH 6.8 TS and use this solution as solution (1).

Replace the medium with 900 mL of phosphate buffer pH 6.8 TS, previously held at 37±0.5 °C. Rotate the basket at 75 revolutions per minute. After 45 minutes, withdraw a sample of 10 mL of the medium through an in-line filter. Dilute 1.0 mL of this solution to 100.0 mL with phosphate buffer pH 6.8 TS and use this solution as solution (2).

Measure the absorbance of solutions (1) and (2) as described under *1.6 Spectrophotometry in the visible and ultraviolet regions* in a cuvette with an optical pathlength of 10 mm at about 265 nm, using phosphate buffer pH 6.8 TS as the blank.

For each of the tablets tested, calculate the total amount of $C_7H_6NNaO_3 \cdot 2H_2O$ in the media, using the absorptivity value of 61.7 ($A_{1cm}^{1\%} = 617$) for Aminosalicylate sodium dihydrate.

Evaluate the results as described under *5.5 Dissolution test for solid oral dosage forms,* Acceptance criteria. The amount of $C_7H_6NNaO_3 \cdot 2H_2O$ released in hydrochloric acid (~3.65 g/L) TS is not more than 10% (Q) and the amount released in phosphate buffer pH 6.8 is not less than 75% (Q) of the amount declared on the label.

Related substances. Prepare the solutions and the mobile phase freshly using low-actinic glassware. Carry out the test as described under *1.14.1 Chromatography,* High-performance liquid chromatography, using the conditions given under "Assay" with the following modification: as a detector, use an ultraviolet spectrophotometer at a wavelength of about 220 nm.

Prepare the following solutions using water R as diluent. For solution (1), powder 20 tablets. Transfer a quantity of the powdered tablets, nominally containing 500 mg of Aminosalicylate sodium dihydrate, into a 500 mL volumetric flask. Add 400 mL and sonicate for 15 minutes. Allow the solution to cool to room temperature, dilute to

volume, mix, centrifuge an aliquot and use the supernatant. For solution (2), dilute 1.0 mL of solution (1) to 200.0 mL.

For solution (3), dissolve 5.0 mg of 3-aminophenol R (impurity A) and 5 mg of mesalazine R (impurity B) and dilute to 100.0 mL. For solution (4), dilute 8.0 mL of solution (3) to 50.0 mL.

Inject 20 µL each of solutions (1), (2) and (4).

Use the chromatogram obtained with solution (4) to identify the peak due to impurity A. The impurities are eluted, if present, at the following relative retention with reference to aminosalicylate (retention time about 17 minutes): impurity A about 0.31 and impurity B about 0.39.

The test is not valid unless, in the chromatogram obtained with solution (4), the resolution between the peaks due to impurity A and 4-aminosalicylate is at least 4.0. Also, the test is not valid unless, in the chromatogram obtained with solution (2), the signal-to-noise ratio of the peak due to aminosalicylate is at least 10.

In the chromatogram obtained with solution (1):

- the area of any peak corresponding to impurity A, when multiplied by a correction factor of 0.62, is not greater than the area of peak due to impurity A (3-aminophenol) in the chromatogram obtained with solution (2) (0.5%).

Assay. Prepare the solutions and the mobile phase freshly using low-actinic glassware. Carry out the test as described under *1.14.1 Chromatography*, High-performance liquid chromatography, using a stainless-steel column (25.0 cm × 4.6 mm) packed with base-deactivated and end-capped particles of silica gel, the surface of which has been modified with base-deactivated particles of silica gel, the surface of which has been modified with chemically-bonded octylsilyl groups (5 µm)[1].

[1] A Hypersil BDS C8 column was found suitable.

Use the following conditions for gradient elution:

Mobile phase A: dissolve 2.2 g of perchloric acid (~1170 g/L) TS and 1.0 g of phosphoric acid (~1440 g/L) TS in water R and dilute to 1000 mL with the same solvent;

Mobile phase B: dissolve 1.7 g of perchloric acid (~1170 g/L) TS and 1.0 g of phosphoric acid (~1440 g/L) TS in acetonitrile R and dilute to 1000 mL with the same solvent.

Time (minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comments
0–15	100	0	Isocratic
15–30	100 to 40	0 to 60	Linear gradient
30–31	40 to 100	60 to 0	Return to initial composition
31–45	100	0	Re-equilibration

Operate with a flow rate of 1.25 mL per minute. As a detector, use an ultraviolet spectrophotometer at a wavelength of about 265 nm.

Prepare the following solutions using water R as diluent. For solution (1), transfer 20 tablets into a 1000 mL volumetric flask. Add 600 mL of diluent and shake for about 30 minutes. Make up to volume and mix . Dilute 5.0 mL of this solution to 1000.0 mL and filter an aliquot. For solution (2), dissolve 50.0 mg of aminosalicylate sodium RS in 100.0 mL. Dilute 10.0 mL of this solution to 100.0 mL.

Inject 10 µL each of solutions (1) and (2).

Measure the areas of the peaks corresponding to aminosalicylate obtained in the chromatograms of solutions (1) and (2) and calculate the percentage content of $C_7H_6NNaO_3 \cdot 2H_2O$ in the tablets using the declared content of $C_7H_6NNaO_4$ in

aminosalicylate sodium RS. Each mg of $C_7H_6NNaO_4$ corresponds to 1.206 mg of $C_7H_6NNaO_3 \cdot 2H_2O$.

Impurities

The impurities limited by the requirements of this monograph include those listed in the monograph on Aminosalicylate sodium dihydrate.

Reagents to be established

3-Aminophenol R

C_6H_7NO

Contains not less than 97.0% of C_6H_7NO

Molecular weight. 109.1

Description. Pale yellowish-brown crystals, sparingly soluble in water.

Melting point. About 122 °C.

Mesalazine R

$C_7H_7NO_3$

Molecular weight. 153.1

Description. Almost white or light grey or light pink powder or crystals.

Melting point. 275 °C to 280 °C, with decomposition.

Reference substances to be established

Aminosalicylate sodium RS

New ICRS to be established.

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