World Health Organization

# AMINOSALICYLATE SODIUM DIHYDRATE

## (AMINOSALICYLATUM NATRICUM DIHYDRICUS)

## Draft proposal for inclusion for *The International Pharmacopoeia*

(15 November 2024)

*DRAFT FOR COMMENTS*

Please submit your comments through the online platform, PleaseReview™ (https://who.pleasereview.net/Main/Default.aspx?action=loaddocument&reviewid=303). If not registered or included in our mailing list, kindly submit your request with your full name, email address and organization/affiliation to jonessi@who.int, nsp@who.int.

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

SCHEDULE FOR THE ADOPTION PROCESS OF DOCUMENT QAS/20.844:

**AMINOSALICYLATE SODIUM DIHYDRATE**

**(AMINOSALICYLATUM NATRICUM DIHYDRICUS)**

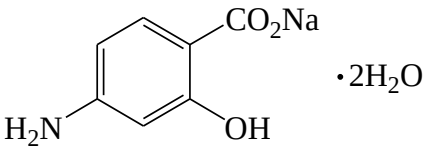
| **Description** | **Date** |
|---|---|
| Draft monograph received from Collaborating Centre. | March 2020 |
| Discussion at the consultation on Screening Technologies, Laboratory Tools and Pharmacopoeial Specifications for Medicines. | May 2020 |
| Discussion at the consultation on Quality Control and Pharmacopoeial Specifications of Medicines | April 2023 |
| Discussion at the consultation on Quality Control and Pharmacopoeial Specifications of Medicines | May 2024 |
| Draft monograph sent out for public consultation. | November 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 DIHYDRATE
# (AMINOSALICYLATUM NATRICUM DIHYDRICUS)

**Molecular formula.** $C_7H_6NNaO_3,2H_2O$

**Relative molecular mass.** 211.2

**Graphic formula.**




**Chemical name.** Sodium 4-amino-2-hydroxybenzoate dihydrate;

**CAS Registry Number**. 6018-19-5.

**Description.** White or almost white, crystalline powder or crystals.

**Solubility.** Freely soluble in water R; sparingly soluble in ethanol (~750 g/L) TS, practically insoluble in dichloromethane R.

**Category.** Antituberculosis.

**Storage.** Aminosalicylate sodium should be kept in a tightly closed container, protected from light.

**Additional information.** Aminosalicylate sodium is slightly hygroscopic.

## Requirements

**Definition.** Aminosalicylate sodium contains not less than 99.0% and not more than 101.0% of $C_7H_6NNaO_3$, calculated with reference to the dried substance.

## Identity tests

- Either tests A and G, tests B and G, or any two of tests C, D, E or E, together with test G, may be applied.

A. Carry out the examination as described under *1.7 Spectrophotometry in the infrared region*. The infrared absorption spectrum is concordant with the spectrum obtained from aminosalicylate sodium RS or with the reference spectrum of aminosalicylate sodium.

B. Carry out the test as described under *1.14.1 Chromatography*, High-performance liquid chromatography, using the conditions and solutions given under "Identity test C" with the following modification: as the detector, use a diode array detector to record the UV spectrum of the principal peak in each chromatogram in the range of 220 nm to 400 nm.

The retention time and the UV spectrum of the principal peak in the chromatogram obtained with solution (A) corresponds to the retention time and 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*, High-performance liquid chromatography, using the conditions given under "Related substances". Prepare the following solutions. For solution (A), dilute 1.0 mL of solution (1) as described under "Related substances" to 10.0 mL with water R. For solution (B), dissolve 10 mg of the aminosalicylate sodium RS in water R and dilute to 100.0 mL with the same solvent.

The retention time of the principal peak in the chromatogram obtained with solution (A) corresponds to the retention time of the peak due to aminosalicylate in the chromatogram obtained with solution (B).

D. Carry out as described under *1.6 Spectrophotometry in the visible and ultraviolet regions*. Transfer 25 mg of the test substance to a 50 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 220 nm and 400 nm, exhibits maxima at 265 and 299 nm.

E. 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 volumes of ethyl acetate R, 1 volume of ethanol (~750 g/L) TS 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), add 5 mL of ethanol (~750 g/L) TS to 10 mg of the test substance, shake and filter. 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).

F. 0.05 g of the test substance yields the reaction described for the identification of primary aromatic amines under *2.1 General identification tests*, producing an intense orange or red precipitate.

G. 0.01 g of the test substance yields reaction A described for the identification of sodium under *2.1 General identification tests*.

**pH value** *(1.13)***.** pH of a freshly prepared 20 mg per mL solution of the test substance in carbon-dioxide-free water R, 6.5-8.5.

**Clarity and colour of solution.** A freshly prepared solution of 2.5 g of the test substance in 25 mL of water R is clear and not more intensely colored than reference solution $B_5$, when compared as described under *1.11.2 Degree of coloration of liquids*, Method II.

**Loss on drying.** Dry to constant weight at 105 °C; it loses not less than 160 mg per g and not more than 180 mg per g.

**Heavy metals.** Use 1.0 g for the preparation of the test solution as described under *2.2.3. Limit test for heavy metals*, Procedure 3; determine the heavy metals content according to method A; not more than 10 µg/g.

**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 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 chemically-bonded octylsilyl groups (5 µm)[1].

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 |

[1] A Hypersil BDS C8column has been found suitable.

| | | | |
|---|---|---|---|
| 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 220 nm.

Prepare the following solutions using water R as the diluent.

For solution (1), dissolve 50 mg of the test substance and dilute to 50.0 mL.

For solution (2), dilute 10.0 mL of solution (1) to 100.0 mL. Dilute 2.0 mL of this solution to 100.0 mL.

For solution (3), dilute 3.0 mL of solution (2) to 20.0 mL.

For solution (4), 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 (5), dilute 5.0 mL of solution (4) to 100.0 mL.

Inject 10 µL each of solutions (1), (2), (3) and (5).

Use the chromatogram obtained with solution (5) to identify the peak due to impurity A and B. 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.

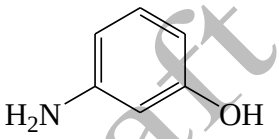
The test is not valid unless, in the chromatogram obtained with solution (5), the resolution between the peaks due to impurity A and impurity B is at least 4.0. Also, the test is not valid unless, in the chromatogram obtained with solution (3), the signal-to-noise ratio of the peak due to aminosalicylate is at least 10.

In the chromatogram obtained with solution (1):

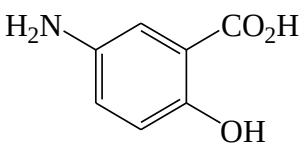
- the area of any peak corresponding to impurity A, when multiplied by a correction factor of 0.62, is not greater than 0.75 times the area of the peak due to aminosalicylate in the chromatogram obtained with solution (2) (0.15%);
- the area of any other impurity peak is not greater than 0.25 times the area of the peak due to aminosalicylate in the chromatogram obtained with solution (2) (0.05%).
- The sum of the areas of all impurity peaks is not greater than the area of the peak due to aminosalicylate in the chromatogram obtained with solution (2) (0.2 %). Disregard any peak with an area of less than the area of the peak due to aminosalicylate in the chromatogram obtained with solution (3) (0.03%).

**Assay.** Carry out the assay as described under *2.7 Nitrite titration.* Dissolve 0.150 g of the test substance in 20 mL of water R. Add 10 mL of a 500 g per L solution of sodium bromide R and 25 mL of glacial acetic acid R. Add 5.0 mL of sodium nitrite (0.1 mol/L) VS rapidly and continue the titration with the same titrant, determining the endpoint potentiometrically. Each mL of sodium nitrite (0.1 mol/L) VS is equivalent to 17.52 mg of $C_7H_6NNaO_3$.

**Impurities**




A. 3-Aminophenol (m-Aminophenol) (synthesis-related impurity, degradation product),




B. 5-Amino-2-hydroxybenzoic acid (mesalazine)(synthesis-related impurity).

## Reagents to be established

### Phosphate buffer, pH 7.0 (0.05 mol/L) TS

*Procedure*. Dissolve 0.681 g of potassium dihydrogen phosphate R in 100.0 mL of water. Adjust the pH using a 7,10 g/L solution of anhydrous disodium hydrogen phosphate R.

## 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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