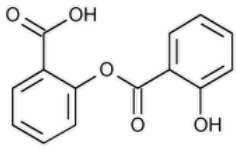
Status: Currently Official on 16-Feb-2025
Official Date: Official as of 01-May-2020
Document Type: USP Monographs
DocId: GUID-5BE0B94A-9F7D-4459-8DC0-66A4BDBF0185_4_en-US
DOI: https://doi.org/10.31003/USPNF_M74393_04_01
DOI Ref: zz5az

Salsalate



$C_{14}H_{10}O_5$ 258.23

Benzoic acid, 2-hydroxy-, 2-carboxyphenyl ester.

Disalicylic acid.

Salicylsalicylic acid.

Salicylic acid, bimolecular ester CAS RN®: 552-94-3; UNII: V9MO595C9I.

» Salsalate contains not less than 98.0 percent and not more than 102.0 percent of total salicylates, expressed as the sum of the percentages of salsalate, salicylic acid, and trisalicylic acid, calculated on the dried basis.

Packaging and storage—Preserve in tight containers.

USP Reference Standards ⟨11⟩—

USP Salsalate RS		
USP Salicylic Acid RS		
USP Trisalicylic Acid RS	$C_{21}H_{14}O_7$	378.34

Change to read:

Identification, ▲Spectroscopic Identification Tests ⟨197⟩, *Infrared Spectroscopy*: 197M▲ (CN 1-May-2020)

Loss on drying ⟨731⟩—Dry it in vacuum at 60° for 3 hours: it loses not more than 0.5% of its weight.

Residue on ignition ⟨281⟩: not more than 0.10%.

Chloride ⟨221⟩—Dissolve 1.4 g in 6 mL of methanol, warming if necessary to effect solution. Dilute with water to 50 mL to precipitate the salsalate, allow to stand for 5 minutes, and filter. A 25-mL portion of the filtrate shows no more chloride than corresponds to 0.20 mL of 0.010 N hydrochloric acid (0.01%).

Sulfate ⟨221⟩—A 17-mL portion of the filtrate prepared for the test for *Chloride* shows no more sulfate than corresponds to 0.50 mL of 0.010 N sulfuric acid (0.05%).

Limit of dimethylaniline—

Internal standard solution—Prepare a solution in methylene chloride containing 0.4 mg of indene per mL.

Standard preparation—Transfer about 50 mg of *N,N*-dimethylaniline, accurately weighed, to a 100-mL volumetric flask, dilute with *Internal standard solution* to volume, insert the stopper securely, and mix.

Test preparation—Transfer about 5 g of Salsalate, accurately weighed, to a 125-mL separator fitted with a cotton pledget in its stem. Add 50 mL of water and 6 mL of 6 N ammonium hydroxide, and swirl until dissolved. Add 5.0 mL of *Internal standard solution*, insert the stopper into the separator, and shake for 1 minute. Keep the separator stoppered, and allow the layers to separate. Loosen the stopper, and drain most of the lower phase into a screw-capped test tube. Use this solution as the *Test preparation*.

Chromatographic system (see *Chromatography ⟨621⟩*)—The gas chromatograph is equipped with a flame-ionization detector, a split injector with a 10:1 split ratio, and a 30-m × 0.53-mm capillary column, the internal wall of which is coated with a 1.0-µm film of phase G42. Maintain the column at 105°, the injector at 250°, and the detector block at 250°, and use helium as the carrier gas, at a flow rate of about 13 mL per minute. Chromatograph the *Standard preparation*, and record the peak responses as directed for *Procedure:* the relative retention times are about 0.75 for indene and 1.0 for *N,N*-dimethylaniline, the resolution, *R,* between the indene peak and the *N,N*-dimethylaniline peak is not less than 2.0, and the relative standard deviation for replicate injections is not more than 3%.

Procedure—[Note—Use peak areas where peak responses are indicated.] Inject equal volumes (about 1 µL) of the *Standard preparation* and the *Test preparation* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Indene elutes before

N,N-dimethylaniline. Calculate the percentage of *N,N*-dimethylaniline in the portion of Salsalate taken by the formula:

$$0.5(C/W)(R_U/R_S)$$

in which *C* is the concentration, in mg per mL, of *N,N*-dimethylaniline in the *Standard preparation*, *W* is the weight, in g, of Salsalate taken to prepare the *Test preparation*, and R_U and R_S are the ratios of the response of the *N,N*-dimethylaniline peak to that of the indene peak obtained from the *Test preparation* and the *Standard preparation*, respectively. The limit is 0.05%.

Isopropyl, ethyl, and methyl salicylates—

Standard stock solution—Prepare a solution in chromatographic *n*-heptane containing 0.20 mg of isopropyl salicylate, 0.50 mg of ethyl salicylate, and 0.50 mg of methyl salicylate per mL.

Standard preparation—Transfer to a suitable screw-capped test tube 2.0 g of Salsalate, add 10 mL of 1 N sodium hydroxide and 2 mL of chromatographic *n*-heptane, shake until dissolved, and allow the layers to separate. Draw off and discard all of the upper layer. To the lower layer add 2.0 mL of *Standard stock solution*, shake for 1 minute, and allow the layers to separate. Use the upper layer as the *Standard preparation*.

Test preparation—Transfer 2.0 g of Salsalate to a suitable screw-capped test tube, add 10 mL of 1 N sodium hydroxide and 2.0 mL of chromatographic *n*-heptane, shake until dissolved, and allow the layers to separate. Use the upper layer as the *Test preparation.*

Chromatographic system (see *Chromatography* ⟨621⟩)—The gas chromatograph is equipped with a flame-ionization detector, a split injector with a 10:1 split ratio, and a 30-m × 0.53-mm capillary column, the internal wall of which is coated with a 1.0-µm film of phase G42. Maintain the column at 120° and the injector and detector block at about 250°. Helium is used as the carrier gas, flowing at the rate of about 13 mL per minute.

Procedure—[NOTE—Use peak areas where peak responses are indicated.] Inject equal volumes (about 1 µL) of the *Standard preparation* and the *Test preparation* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. The relative retention times are about 0.65 for methyl salicylate, 0.9 for ethyl salicylate, and 1.0 for isopropyl salicylate. The response of any isopropyl salicylate peak obtained from the *Test preparation* is not greater than that obtained from the *Standard preparation* (0.02%), the response of any ethyl salicylate peak obtained from the *Test preparation* is not greater than that obtained from the *Standard preparation* (0.05%), and the response of any methyl salicylate peak obtained from the *Test preparation* is not greater than that obtained from the *Standard preparation* (0.05%).

Chromatographic purity—Using the chromatograms obtained in the *Assay*, calculate the percentage of each impurity, other than salicylic acid and trisalicylic acid, in the portion of Salsalate taken by the formula:

$$10{,}000(C/W)(r_U/r_S)$$

in which *C* is the concentration, in mg per mL, of USP Salsalate RS in the *Salsalate standard preparation*, *W* is the weight, in mg, of Salsalate taken to prepare the *Assay stock solution*, r_U is the response of the particular impurity peak obtained from the *Assay stock solution*, and r_S is the salsalate peak response obtained from the *Salsalate standard preparation:* not more than 0.2% of each other impurity is found.

Related compounds—The percentages of salicylic acid and trisalicylic acid, determined as directed in the *Assay*, do not exceed 0.5% and 2.5%, respectively.

Assay—

Mobile phase—Prepare a suitable filtered and degassed mixture of methanol, water, and phosphoric acid (650:350:1), and adjust with phosphoric acid or 1 N sodium hydroxide, if necessary, to a pH of 3.1. Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Diluent—Prepare a mixture of water, acetonitrile, and phosphoric acid (540:460:1).

Salsalate standard preparation—Dissolve an accurately weighed quantity of USP Salsalate RS in *Diluent* to obtain a stock solution having a known concentration of about 1 mg per mL. Transfer 2.0 mL of this solution to a 100-mL volumetric flask, dilute with *Diluent* to volume, and mix. This solution contains about 0.02 mg per mL.

Salicylic acid standard preparation—Dissolve an accurately weighed quantity of USP Salicylic Acid RS in *Diluent* to obtain a stock solution having a known concentration of about 0.5 mg per mL. Transfer 1.0 mL of this solution to a 100-mL volumetric flask, dilute with *Diluent* to volume, and mix. This solution contains about 0.005 mg of USP Salicylic Acid RS per mL.

Trisalicylic acid standard preparation—Dissolve an accurately weighed quantity of USP Trisalicylic Acid RS in *Diluent* to obtain a stock solution having a known concentration of about 0.5 mg per mL. Transfer 5.0 mL of this solution to a 100-mL volumetric flask, dilute with *Diluent* to volume, and mix. This solution contains about 0.025 mg of USP Trisalicylic Acid RS per mL.

Resolution solution—Prepare a solution in *Diluent* containing about 0.02 mg of USP Salsalate RS per mL, 0.02 mg of USP Salicylic Acid RS per mL, and 0.04 mg of USP Trisalicylic Acid RS per mL.

Assay stock solution—Transfer about 100 mg of Salsalate, accurately weighed, to a 100-mL volumetric flask, dilute with *Diluent* to volume, and mix. Sonicate if necessary to effect the solution.

Assay preparation—Transfer 2.0 mL of the *Assay stock solution* to a 100-mL volumetric flask, dilute with *Diluent* to volume, and mix.

Chromatographic system (see Chromatography ⟨621⟩)—The liquid chromatograph is equipped with a 236-nm detector and a 4-mm × 15-cm column that contains 5-µm packing L7. The flow rate is about 1.5 mL per minute. Chromatograph the *Resolution solution*, and record the peak responses as directed for *Procedure:* the relative retention times are about 0.55 for salicylic acid, 1.0 for salsalate, and 1.5 for trisalicylic acid, and the resolution, *R,* between the salicylic acid and salsalate peaks and between the salsalate and trisalicylic acid peaks is not less than 2.0. Chromatograph the *Salicylic acid standard preparation*, and record the peak responses as directed for *Procedure:* the relative standard deviation of the salicylic acid peak responses for replicate injections is not more than 2.0%.

Procedure—Separately inject equal volumes (about 10 µL) of the *Salsalate standard preparation*, the *Salicylic acid standard preparation*, the *Trisalicylic acid standard preparation*, the *Assay stock solution*, and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. [NOTE—Continue chromatography after each injection for a period of time not less than the retention time of trisalicylic acid.] Calculate the percentage of salicylic acid ($C_7H_6O_3$) in the portion of Salsalate taken by the formula:

$$10{,}000(C/W)(r_U/r_S)$$

in which C is the concentration, in mg per mL, of USP Salicylic Acid RS in the *Salicylic acid standard preparation, W* is the weight, in mg, of the portion of Salsalate taken, and r_U and r_S are the responses of the salicylic acid peak obtained from the *Assay stock solution* and the *Salicylic acid standard preparation*, respectively. Calculate the percentage of trisalicylic acid ($C_{21}H_{14}O_7$) in the portion of Salsalate taken by the formula:

$$10{,}000(C/W)(r_U/r_S)$$

in which C is the concentration, in mg per mL, of USP Trisalicylic Acid RS in the *Trisalicylic acid standard preparation*, and r_U and r_S are the responses of the trisalicylic acid peaks obtained from the *Assay stock solution* and the *Trisalicylic acid standard preparation*, respectively. Calculate the percentage of salsalate ($C_{14}H_{10}O_5$) in the portion of Salsalate taken by the formula:

$$500{,}000(C/W)(r_U/r_S)$$

in which C is the concentration, in mg per mL, of USP Salsalate RS in the *Salsalate standard preparation*, and r_U and r_S are the salsalate peak responses obtained from the *Assay preparation* and the *Salsalate standard preparation*, respectively.

Auxiliary Information - Please check for your question in the FAQs before contacting USP.

Topic/Question	Contact	Expert Committee
SALSALATE	Documentary Standards Support	SM22020 Small Molecules 2
REFERENCE STANDARD SUPPORT	RS Technical Services RSTECH@usp.org	SM22020 Small Molecules 2

Chromatographic Database Information: Chromatographic Database

Most Recently Appeared In:
Pharmacopeial Forum: Volume No. Information currently unavailable

Current DocID: GUID-5BE0B94A-9F7D-4459-8DC0-66A4BDBF0185_4_en-US
DOI: https://doi.org/10.31003/USPNF_M74393_04_01
DOI ref: zz5az