Methyl Salicylate

Type of Posting	Revision Bulletin
Posting Date	28–July–2017
Official Date	01–Aug–2017
Expert Committee	Excipient Monographs 1
Reason for Revision	Compliance

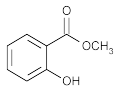
In accordance with the Rules and Procedures of the 2015-2020 Council of Experts, the Excipient Monographs 1 Expert Committee has revised the Methyl Salicylate monograph. The purpose for the revision is to change the upper limit of the acceptance criteria in the *Assay* from NMT 100.5% to NMT102.0% to allow for a higher variability of the HPLC method compared with that of the original titration Assay. The HPLC method became official in the *Second Supplement* to *USP 38–NF 33.*

The Methyl Salicylate Revision Bulletin supersedes the currently official monograph. The Revision Bulletin will be incorporated in the *First Supplement* to *USP 41–NF 36*.

.

Should you have any questions, please contact Dr. Galina Holloway, Senior Scientific Liaison (301–816–8133 or gvh@usp.org).

Methyl Salicylate



$C_8H_8O_3$ 152.15
Benzoic acid, 2-hydroxy-, methyl ester;
Methyl salicylate [119-36-8].

DEFINITION

Change to read:

Methyl Salicylate is produced synthetically or is obtained by maceration and subsequent distillation with steam from the leaves of *Gaultheria procumbens* L. (Fam. Ericaceae) or from the bark of *Betula lenta* L. (Fam. Betulaceae). It contains NLT 98.0% and NMT •102.0%• (RB 1-Aug-2017) of methyl salicylate ($C_8H_8O_3$).

IDENTIFICATION

- **A. INFRARED ABSORPTION ⟨197F⟩**
- **B. CHROMATOGRAPHIC IDENTITY**
  Analysis: Proceed as directed in the *Assay*.
  Acceptance criteria: The retention time of the major peak of the *Sample solution* corresponds to that of the *Standard solution*.

ASSAY

Change to read:

- **PROCEDURE**
  Mobile phase: Methanol and 0.1% phosphoric acid (55:45)
  Diluent: Methanol
  System suitability solution: 150 µg/mL of USP Methyl Salicylate RS and 3 µg/mL of USP Methyl Salicylate Related Compound A RS in *Diluent*
  Standard solution: 150 µg/mL of USP Methyl Salicylate RS in *Diluent*
  Sample solution: 150 µg/mL of Methyl Salicylate in *Diluent*
  Chromatographic system
  (See *Chromatography* ⟨621⟩, *System Suitability*.)
  Mode: LC
  Detector: UV 237 nm
  Column: 4.6-mm × 7.5-cm; 3.5-µm packing L7
  Column temperature: Ambient
  Flow rate: 1.0 mL/min
  Injection volume: 10 µL
  Run time: 7 min
  System suitability
  Samples: *System suitability solution* and *Standard solution*
  [NOTE—The relative retention times for methyl salicylate and dimethyl 4-hydroxyisophthalate are 1.0 and 1.2, respectively.]
  Suitability requirements
  Resolution: NLT 1.5 between methyl salicylate and dimethyl 4-hydroxyisophthalate, *System suitability solution*
  Tailing factor: NMT 1.5 for the methyl salicylate peak, *Standard solution*
  Relative standard deviation: NMT 0.5% for the methyl salicylate peak, *Standard solution*
  Analysis
  Samples: *Standard solution* and *Sample solution*
  Calculate the percentage of methyl salicylate in the portion of Methyl Salicylate taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times 100$$

r_U = peak response from the *Sample solution*
r_S = peak response from the *Standard solution*
C_S = concentration of USP Methyl Salicylate RS in the *Standard solution* (µg/mL)
C_U = concentration of Methyl Salicylate in the *Sample solution* (µg/mL)

Acceptance criteria: 98.0%–•102.0%• (RB 1-Aug-2017)

IMPURITIES

Delete the following:

•• **HEAVY METALS,** *Method II* ⟨**231**⟩**:** NMT 20 µg/g• (Official 1-Jan-2018)

- **LIMIT OF SALICYLIC ACID AND DIMETHYL 4-HYDROXYISOPHTHALATE**
  Mobile phase, Diluent, Sample solution, and **Chromatographic system:** Proceed as directed in the *Assay*.
  Standard solution: 0.15 µg/mL of USP Salicylic Acid RS, 0.15 µg/mL of USP Methyl Salicylate RS, and 0.75 µg/mL of USP Methyl Salicylate Related Compound A RS in *Diluent*
  System suitability
  Sample: *Standard solution*
  [NOTE—The relative retention times for salicylic acid, methyl salicylate, and dimethyl 4-hydroxyisophthalate are 0.6, 1.0, and 1.2, respectively.]
  Suitability requirements
  Resolution: NLT 4 between salicylic acid and methyl salicylate; NLT 2 between methyl salicylate and dimethyl 4-hydroxyisophthalate
  Relative standard deviation: NMT 3% for all three peaks
  Analysis
  Samples: *Sample solution* and *Standard solution*
  Calculate the percentage of each individual impurity in the portion of Methyl Salicylate taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times 100$$

r_U = peak response of salicylic acid or dimethyl 4-hydroxyisophthalate from the *Sample solution*
r_S = peak response of salicylic acid or dimethyl 4-hydroxyisophthalate from the *Standard solution*
C_S = concentration of USP Salicylic Acid RS or USP Methyl Salicylate Related Compound A RS in the *Standard solution* (µg/mL)
C_U = concentration of Methyl Salicylate in the *Sample solution* (µg/mL)

Acceptance criteria
Salicylic acid: NMT 0.1%
Dimethyl 4-hydroxyisophthalate: NMT 0.5%

SPECIFIC TESTS

- **SOLUBILITY IN 70% ALCOHOL:** One volume of synthetic Methyl Salicylate dissolves in seven volumes of 70% alcohol. One volume of natural Methyl Salicylate dissolves in seven volumes of 70% alcohol, the solution shows NMT a slight cloudiness.
- **SPECIFIC GRAVITY** ⟨**841**⟩**:** 1.180–1.185 for the synthetic variety; 1.176–1.182 for the natural variety

- **OPTICAL ROTATION** ⟨**781A**⟩**,** *Procedures, Angular Rotation***:** Synthetic Methyl Salicylate and that from *Betula lenta* are optically inactive. Methyl Salicylate from *Gaultheria procumbens* is slightly levorotatory, the angular rotation not exceeding –1.5° in a 100-mm tube.

ADDITIONAL REQUIREMENTS

- **PACKAGING AND STORAGE:** Preserve in tight containers.
- **LABELING:** Label it to indicate whether it was made synthetically or distilled from either of the plants of *Gaultheria procumbens* or *Betula lenta*.

- **USP REFERENCE STANDARDS** ⟨**11**⟩
  USP Methyl Salicylate RS
  USP Methyl Salicylate Related Compound A RS
  Dimethyl 4-hydroxyisophthalate.
  $C_{10}H_{10}O_5$ 210.18
  USP Salicylic Acid RS

C181841-M52100-EXC12015; C182124-M52100-EXC12015; C182797_M52100-EXC12015; C186974-M52100-EXC12015, Rev. 0 20170728