Methyl Salicylate

Technical Package

Drug Master File
CTD Format Module – 3.2.S
Open Part

Version 1
MAY 2010

Compiled on behalf of JQC (Huayin) Pharmaceutical Co., Ltd
Huayin City, Shaanxi, P. R. China

Table of Contents

3.2.S.1 General Information

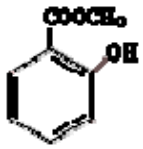
3.2.S.1.1 Nomenclature

Generic Name: Methyl Salicylate

Chemical Name: Methyl 2-hydroxybenzoate

CAS No: [119-36-8]

3.2.S.1.2 Structure



Molecular Formula: $C_8H_8O_3$ Molecular Weight: 152.1

3.2.S.1.3 General Properties

According to the USP, Methyl Salicylate A colorless or slightly yellow liquid. It is solute in alcohol, ether, slightly soluble in water, easy to change color in the air.

The approximate solubilities of the Active Pharmaceutical Ingredient are indicated by the descriptive terms in the accompanying table:

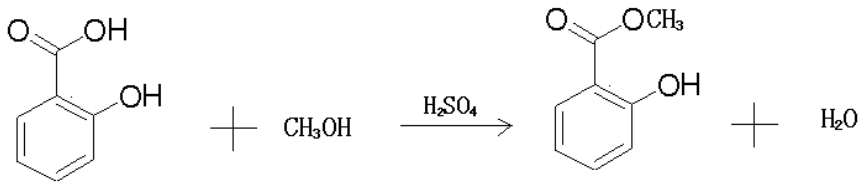
DESCRIPTIVE TERM	PARTS OF SOLVENT REQUIRED FOR 1 PART OF SOLUTE
Freely soluble	From 1 to 10
Soluble	From 10 to 30
Slightly soluble	From 100 to 1000

-Odor: Characteristic odor.
-Solubility: Sparingly soluble in water.
-Specific Gravity: 1.180-1.185
-pH: No information found.
-% Volatiles by volume @ 21C (70F): 100
-Boiling Point: 222.2C (432F)
-Melting Point: -8.3C (18F)
-Vapor Density (Air=1): 5.24
-Vapor Pressure (mm Hg): 1 @ 54C (129F)
-Evaporation Rate (BuAc=1): No information found.
- Oral rat LD50: 887 mg/kg. Irritation data: skin rabbit 500 mg/24 Hr Moderate; eye rabbit 500 mg/24 Hr Mild. Investigated as a mutagen, reproductive effector.

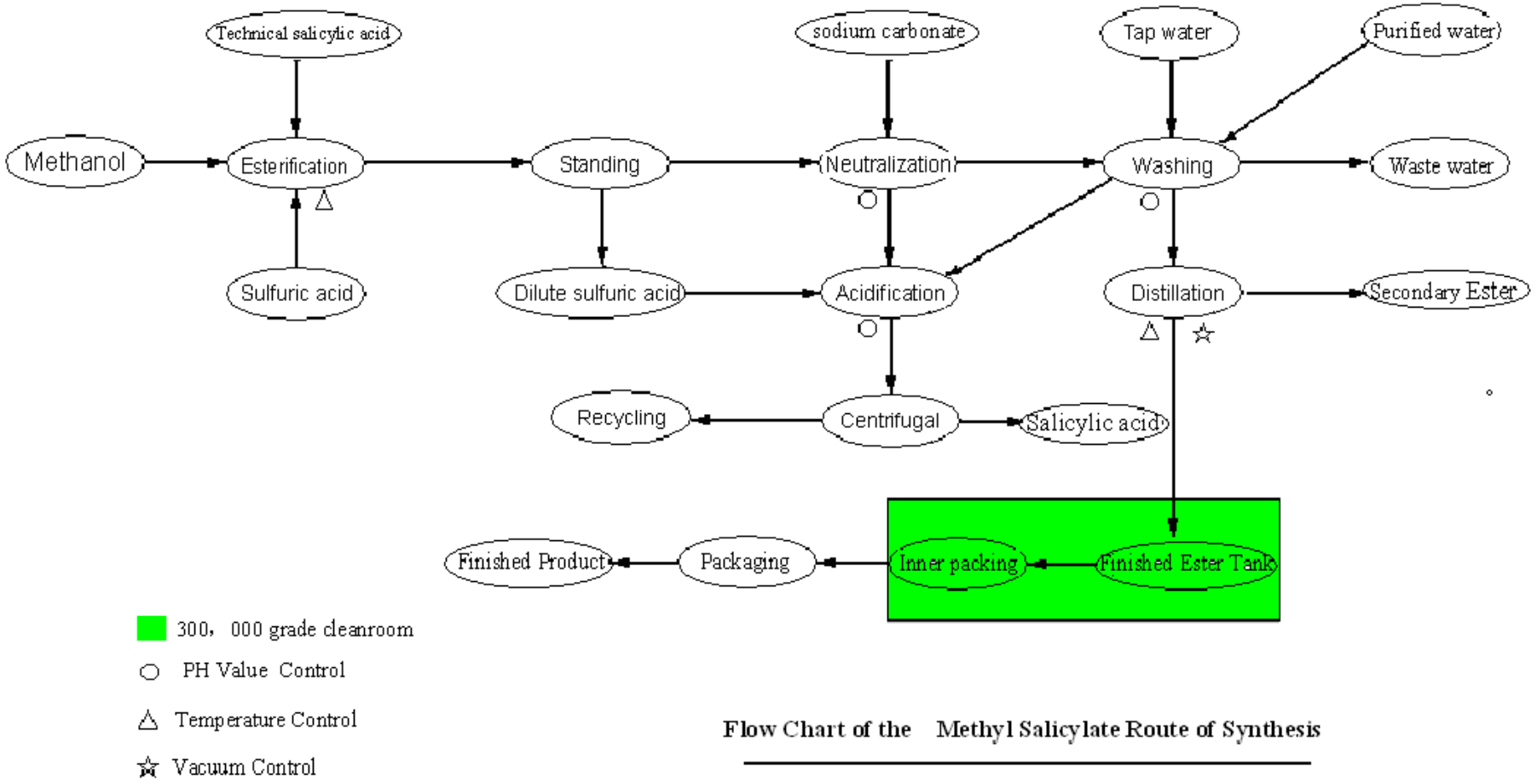
3.2.S.2 Manufacture

3.2.S.2.1 Description of manufacturing process

Organic Reaction Equation:



Flow Chart of the Methyl Salicylate Route of Synthesis



Flow Chart of the Methyl Salicylate Route of Synthesis

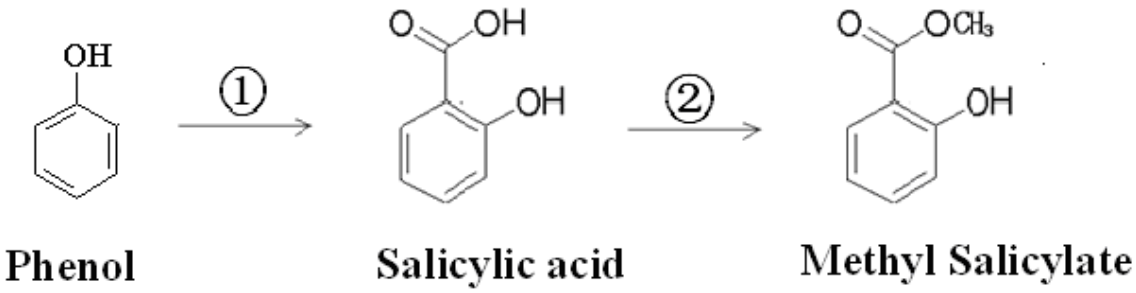
3.2.S.3 Characterization

3.2.S.3.1 Elucidation of Structure

Infrared and ultraviolet absorption spectroscopy is performed on Methyl Salicylate by JQC (Huayin) Pharmacuetical Co., Ltd as part of the routine release testing. The IR and UV spectra of the sample have been compared to spectra of the Reference Standard. The spectra are concordant (see Attachment 1).

3.2.S.3.2 Impurities

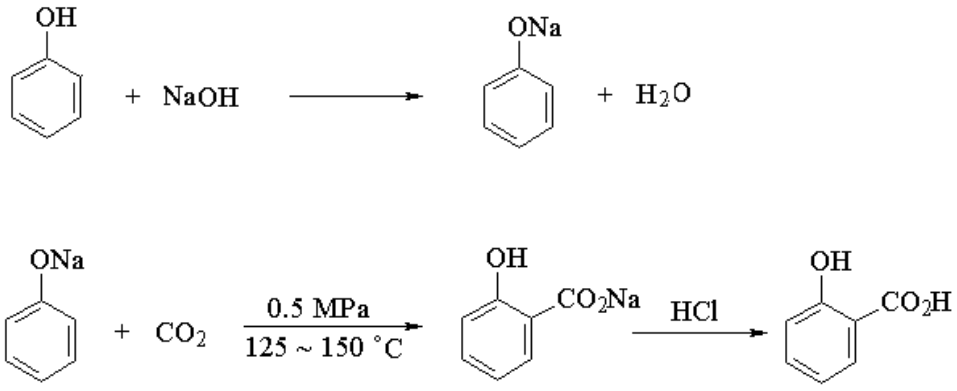
Process impurities (related substances):



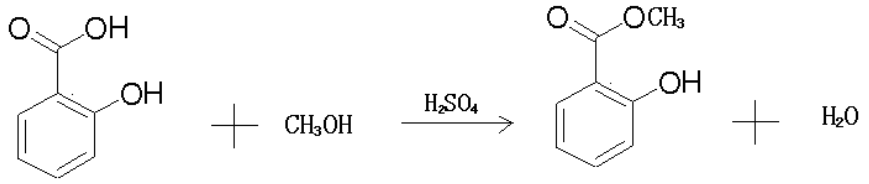
Phenol	Salicylic acid	Methyl Salicylate
	4-Hydroxy-benzoic acid	Methyl 4-hydroxybenzoate
	4-Hydroxyisophthalic acid	Dimethyl 4-hydroxyisophthalate

Main reaction:

Step 1: Phenol, form Salicylic acid

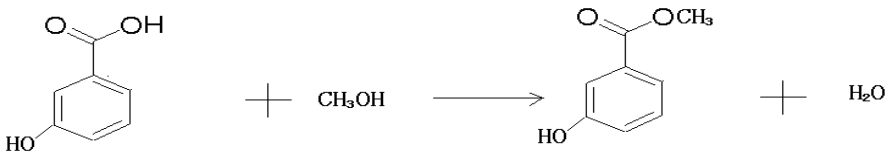


Step 2: Salicylic acid, form Methyl Salicylate

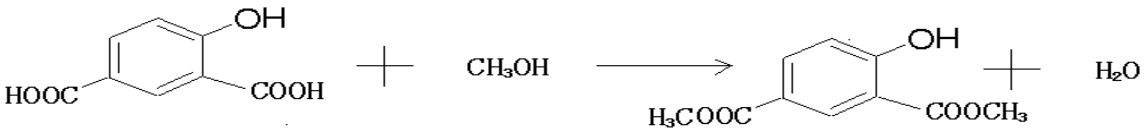


Side reactions:

1. 4-hydroxybenzoic acid, form methyl p-hydroxybenzoate

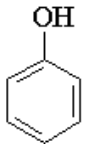


2. 4-Hydroxyisophthalic acid, form dimethyl 4-hydroxyisophthalate

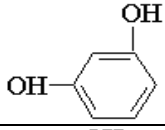
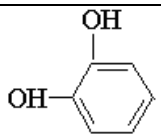


Additional discussion on raw material, intermediate and related impurities:

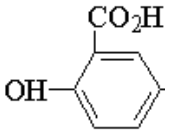
1. Raw material: Phenol



   a. It is difficult to find out related process impurities in industrial grade phenol
   b. The degradation products of phenol at industrial grade mainly are hydroquinone, hydroxyphenol and pyrocatechol.

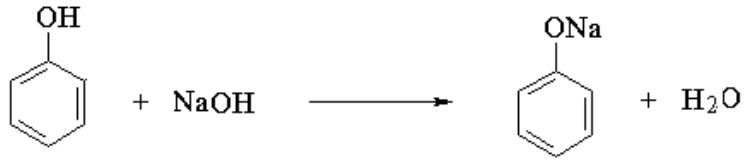
Chemical name	Structure	Source
Hydroquinone		Intermediate from degradation
Hydroxyphenol		Intermediate from degradation
Pyrocatechol		Intermediate from degradation
Quinone	Unknown structure	Intermediate from degradation

2. Salicylic acid

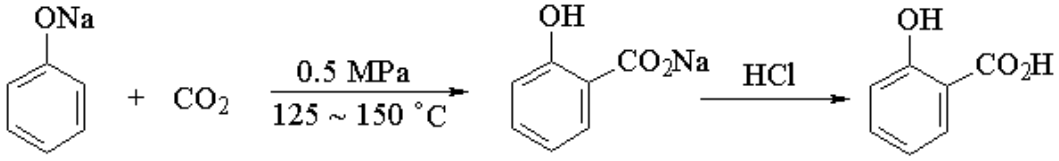


Main reaction for synthesis of Salicylic acid

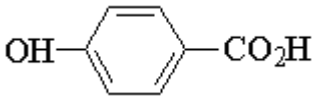
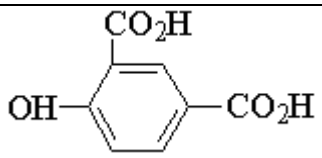
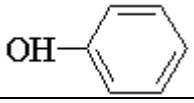
Stage 2.1



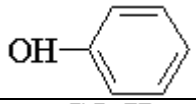
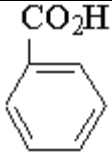
Stage 2.2



a.Related substances (process impurities):

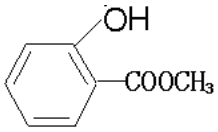
Chemical name	Structure	Source
Hydroxybenzoic acid		Intermediate
4-Hydroxyisophthalic acid		Intermediate
Phenol		Degradation intermediate, raw material
Other impurities	unknown	Degradation product

b.Degradation products:

Chemical name	Structure	Source
Phenol		Degradation intermediate, raw material
Benzoic acid		Degradation intermediate

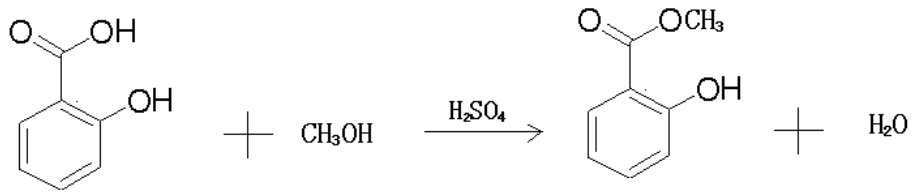
All above information is from literature, not from stability study.

3. Methyl Salicylate

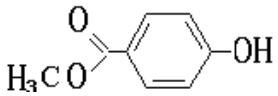
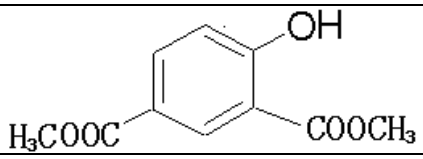
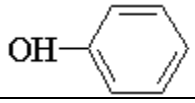
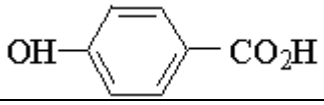


Main reaction for synthesis of Methyl Salicylate

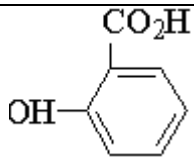
Stage 3.1



a. Related substances (process impurities):

Chemical name	Structure	Source
4-Hydroxybenzoic acid methyl ester		Intermediate
Dimethyl 4-hydroxyisophthalate		Intermediate
Phenol		Raw material
4-Hydroxybenzoic acid		Intermediate of raw material

b. Degradation impurity

Chemical name	Structure	Source
2-Hydroxybenzoic acid		Degradation intermediate

a. Degradation product:

Chemical name	Structure	Source
No	No	No

b. Inorganic impurities:

Name	Raw material and catalyst	Limit	Specification
Heavy metals	Sodium Pyrosulfite	≤20ppm	USP30

c. Residual solvents:

According with USP30 appendix of Organic volatile impurities Method Ⅳ (467)

Name	Raw material and catalyst	Limit	Specification
Methanol	Raw material/ Methanol	≤3000 ug/g	USP30

3.2.S.4 Control of Drug Substance (API)

3.2.S.4.1 Specifications

Methyl Salicylate is tested according to the United States Pharmacopoeia (USP) as follows:

Analytical Test	Specifications
Characters / Description (USP30)	Colorless or slightly yellow liquid
Solubility in 70% alcohol(USP30)	The solution having not more than a slight cloudiness
Identification (USP30) Color reaction	The resulting mixture has a deep violet color
Specific gravity(USP30)	1.180-1.185
Angular rotation(USP30)	Is optically inactive
Refractive index(USP30)	1.535-1.538（20℃）
Heavy Metals (USP30)	20ug per g
Organic volatile impurities(USP30)	Meets the requirements
Assay by titration (USP30)	98.0% to 100.5%

3.2.S.4.2 Analytical Procedures

Methyl Salicylate is tested according to the current United States Pharmacopoeia (USP) as follows:

Methyl Salicylate is produced synthetically,it contains not less than 98.0% and not more than 100.5% of $C_8H_8O_3$,

Packaging and storage - Preserve in tight containers.

Labeling—label it to indicate whether it was made synthetically or distilled from either of the plants mentioned above

Solubility in 70% alcohol-one volume of synthetic methyl salicylate dissolves in 7 volumes of 70% alcohol,
Identification:
Shake 1 drop with about 5ml of water, and add 1 drops of ferric chloride TS: a violet color develops.

Specific gravity（841）：between 1.180 and 1.185 for the synthetic variety;

Angular rotation(781):Synthetic methyl salicylate and that from betula are optically inactive.

Refractive index (831):between 1.535 and 1.538 at 20℃.

Heavy metals, Method II <231>:20ug per g.

Organic volatile impurities MethodⅣ(467):meets the requirements

Assay:place about 2g of methyl salicylate,accurately weighed,in a flask,add 40.0 ml of 1N sodium hydroxide VS,and boil gently under a reflux condenser for 2 hours,cool, rinse the condenser and the sides of the flask with a few ml of water,add phenolphthalein TS,and titrate the excess alkali with 1N sulfuric acid VS.perform a blank determination (see Residual Titrations under Titrimetry<541>),Each ml of 0.1 sodium hydroxide corresponds to 152.2mg of $C_8H_8O_3$.

3.2.S.4.3 Validation of analytical procedures

All the test methods for Methyl Salicylate are compendial and as such are deemed to be validated.

3.2.S.4.4 Batch Analysis

Analytical Test	Specifications	Batch J1009002	Batch J1009003
Manufacturing Date	-	2010.09.13	2010.09.14
Characters / Description	Colorless or slightly yellow liquid	Meets the requirements	Meets the requirements
Solubility in 70% alcohol	The solution having not more than a slight cloudiness	not more than a slight cloudiness	not more than a slight cloudiness
Identification Color reaction	The resulting mixture has a deep violet color	Meets the requirements	Meets the requirements
Specific gravity	1.180-1.185	1.183	1.182
Angular rotation	It is optically inactive	It is optically inactive	It is optically inactive
Refractive index	1.535-1.538（20℃）	1.5367	1.5366
Heavy Metals	20ug per g	＜20ppm	＜20ppm
Organic volatile impurities	Meets the requirements	＜3000ppm	＜3000ppm
Assay by titration	98.0% to 100.5%	99.06%	99.03%

Certificates of Analysis for the two batches can be found in Attachment 3.

3.2.S.4.5 Justification of Specifications (API)

All specifications are as per USP requirements.

3.2.S.5 Reference Standards or Materials

A Methyl Salicylate Working Standard has been qualified for use in routine release testing. A copy of the COA for the Working Standard can be found in Attachment 4.

3.2.S.6 Container Closure System

The following packaging materials are used for the packaging of Methyl Salicylate API: HDPE small drum (primary packaging) and HDPE big drum.

The specifications for the HDPE drum are as follows:

Standard Operation Procedure of
Huayin Jinqiancheng Pharmaceutical Co., Ltd

Code number:

Code number	JQC-SDC-41-015	Document name	Specification of HDPE drum			Version number	2nd version
Drafted by Department	Quality department	Drafted by		Reviewed by		Approved by	
Effective since		Drafted on		Reviewed on		Approved on	

Objective: This SOP is to specify the size, technical standard, test methods, mark, storage requirements of the HDPE drum for primary packaging use.

Range: This SOP applies to the procedure for purchasing and using of the HDPE drum for primary packaging purpose.

Responsibility: Quality department, production department, material control department

Content:

1. Property and size
   1.1 property: Made of nontoxic HDPE (High Density Polyethylene)
   1.2 size and accepted deviation, please see table 1

Table 1

Packing quantity (kg)	Size (mm)	Deviation (mm)
25kg	900×520×0.08	(Length±5)×(Width±5)× (thickness±0.05)
230kg	580×920	(Diameter±5) ×（Height±10）

2. Technical requirements
   Appearance: the drum should be smooth and level. The drum should not be over thick or over thin. The thickness is 0.8mm, and the acceptable deviation is ±0.05mm.
   Outer packaging: the PE drum should be sealed to protect the drum inside from pollution.

3. Test methods
   3.1 Appearance check: Should be good without damage and pollution.
   3.2 Sampling should be carried out in sampling hut and the hut should meet the requirement of class 300,000.
   3.3 Size check: The Diameter and height should be measured by the stainless ruler with the minimum scale of 0.5mm.

3.4 The drum produced in one time is regarded as one batch. Take 100 sample drum and check the outer packaging, appearance and size according to the acceptance criteria, the pass rate should be no less than 97%.
3.5 If either one test of above three on the drum fails the preset pass rate, the drums should re-sampled and retested. If it still fails, then this batch should be rated as unqualified.
3.6 The breakage rate should be no more than 0.5%.

4 Label, packaging, transportation, storage:
4.1 After releasing, the PE drums should be marked with new labels with number before entering the warehouse.
4.2 Collision and toss should be avoided when loading the PE drums or transferring them to workshop.
4.3 The PE drums should be protected against dampness and kept clean during the storage.

3.2.S.7 Stability

Based on the results to date for 6 months accelerated and 36 months long-term (3 batches), a 36 month (3 year) re-test date has been assigned.

Stability Test Results:
See Attachment 5.

GMP Certificate

JQC (Huayin) Pharmaceutical Co., Ltd's GMP certificate issued by the Chinese SFDA can be found in Attachment 6.