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Warfarin Sodium Tablets

DEFINITION
Warfarin Sodium Tablets contain NLT 95.0% and NMT 105.0% of the labeled amount of warfarin sodium ($C_{19}H_{15}NaO_4$).

IDENTIFICATION

- **A.** The retention time of the major peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay*.
- **B.** **Spectroscopic Identification Tests ⟨197⟩, *Infrared Spectroscopy*: 197K**

Sample: Triturate a quantity of finely powdered Tablets, equivalent to about 200 mg of warfarin sodium, with 50 mL of water, centrifuge, and filter the supernatant. Extract with 50 mL of ether, transfer the aqueous layer to a second separator, and discard the ether. Adjust with hydrochloric acid to a pH of less than 3, using short-range pH indicator paper, and extract with 50 mL of chloroform. Transfer the chloroform layer to another separator, extract with 50 mL of sodium hydroxide solution (1 in 250), and discard the chloroform. Transfer the aqueous layer to a beaker, and adjust with hydrochloric acid to a pH of less than 3 (using the pH indicator paper) to precipitate the warfarin. Stir the mixture, and allow the precipitate to coagulate. Filter, and wash the precipitate with four, 5-mL portions of water. If the precipitate is not white or practically white, dissolve it in a minimum volume of sodium hydroxide solution (1 in 250), dilute with water to 50 mL, and repeat the foregoing procedure, beginning with "Extract with 50 mL of ether." Dry the warfarin under vacuum over phosphorus pentoxide for 4 h.

ASSAY

- **Procedure**

Buffer: Transfer 1.36 g of monobasic potassium phosphate to a 200-mL volumetric flask, and dissolve in 50 mL of water. Add 39.1 mL of 0.2 N sodium hydroxide, and dilute with water to volume. Adjust with sodium hydroxide or phosphoric acid to a pH of 7.4 ± 0.1.

Diluent: Acetonitrile and *Buffer* (15:85)

Mobile phase: Methanol, glacial acetic acid, and water (68:1:32)

Standard stock solution: 0.31 mg/mL of USP Warfarin RS prepared as follows. Transfer USP Warfarin RS to a suitable volumetric flask, and dissolve in 0.1 N sodium hydroxide equivalent to 39% of the final volume. Add 0.2 M monobasic potassium phosphate, equivalent to 25% of the final volume, and dilute with water to volume.

Standard solution: Transfer 15.0 mL of *Standard stock solution* into a 50-mL volumetric flask, and dilute with *Diluent* to volume.

Sample solution: Nominally 0.1 mg/mL of warfarin sodium in *Diluent* prepared as follows. Weigh, and finely powder NLT 20 Tablets. Transfer an accurately weighed portion of the powder, equivalent to about 5 mg of warfarin sodium, to a 50-mL volumetric flask, and add about 30 mL of *Diluent*. Sonicate for 10 min, and then shake by mechanical means for 60 min. Dilute with *Diluent* to volume, and filter.

Chromatographic system

(See *Chromatography ⟨621⟩, System Suitability*.)

Mode: LC

Detector: UV 280 nm

Column: 4.6-mm × 25-cm; packing L7

Flow rate: 1.4 mL/min

Injection volume: 20 µL

System suitability

Sample: *Standard solution*

Suitability requirements

Relative standard deviation: NMT 1.0%

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of warfarin sodium ($C_{19}H_{15}NaO_4$) in the portion of Tablets taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times (M_{r1}/M_{r2}) \times 100$$

r_U = peak response of warfarin from the *Sample solution*

r_S = peak response of warfarin from the *Standard solution*

C_S = concentration of USP Warfarin RS in the *Standard solution* (mg/mL)

C_U = nominal concentration of warfarin sodium in the *Sample solution* (mg/mL)

M_{r1} = molecular weight of warfarin sodium, 330.31

M_{r2} = molecular weight of warfarin, 308.33

Acceptance criteria: 95.0%–105.0%

PERFORMANCE TESTS

• **Dissolution ⟨711⟩**

Medium: Water; 900 mL

Apparatus 2: 50 rpm

Time: 30 min

Mobile phase: Prepare as directed in the *Assay*.

Standard solution: USP Warfarin RS in water, having a known concentration of 0.0008*L* mg/mL, *L* being the labeled amount, in mg, of warfarin sodium in the Tablets. [Note—Use a small amount of 0.1 N sodium hydroxide to aid in dissolution.]

Sample solution: Pass a portion of the solution under test through a suitable filter.

Chromatographic system: Proceed as directed in the *Assay* except the *Injection volume*.

Injection volume: 40 µL

System suitability: Proceed as directed in the *Assay*.

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of warfarin sodium ($C_{19}H_{15}NaO_4$) dissolved:

$$\text{Result} = (r_U/r_S) \times C_S \times V \times (M_{r1}/M_{r2}) \times (1/L) \times 100$$

r_U = peak response of warfarin from the *Sample solution*

r_S = peak response of warfarin from the *Standard solution*

C_S = concentration of USP Warfarin RS in the *Standard solution* (mg/mL)

V = volume of *Medium*, 900 mL

M_{r1} = molecular weight of warfarin sodium, 330.31

M_{r2} = molecular weight of warfarin, 308.33

L = label claim (mg/Tablet)

Tolerances: NLT 80% (*Q*) of the labeled amount of warfarin sodium ($C_{19}H_{15}NaO_4$) is dissolved.

• **Uniformity of Dosage Units ⟨905⟩:** Meet the requirements

IMPURITIES

• **Organic Impurities**

Diluent: Methanol and water (25:75). Alternatively, a mixture of acetonitrile and water (25:75) can be used.

Mobile phase: Methanol, tetrahydrofuran, glacial acetic acid, and water (57:1:1:42)

Standard stock solution: 0.126 mg/mL of USP Warfarin RS prepared as follows. Transfer USP Warfarin RS to a suitable volumetric flask, and add 0.1 N sodium hydroxide and methanol equivalent to 2% and 25% of the final volume, respectively. Sonicate, if necessary, to dissolve. Dilute with water to volume.

Standard solution (for 1-mg Tablets)**:** 1.0 µg/mL of USP Warfarin RS in *Diluent* from *Standard stock solution*

Standard solution (for other strengths)**:** 2.0 µg/mL of USP Warfarin RS in *Diluent* from *Standard stock solution*

System suitability stock solution: 0.4 mg/mL of USP Warfarin Related Compound A RS in methanol

System suitability solution: 2.0 µg/mL of each of USP Warfarin RS and USP Warfarin Related Compound A RS in *Diluent* from *Standard stock solution* and *System suitability stock solution*

Sample solution (for 1-mg Tablets)**:** Nominally 0.4 mg/mL of warfarin sodium in *Diluent* prepared as follows. Transfer 10 Tablets into a suitable volumetric flask, dissolve Tablets in *Diluent* by sonicating for 10 min and shaking for 60 min. Dilute with *Diluent* to volume. Pass through a suitable filter, and discard the first few mL.

Sample solution (for other strengths)**:** Nominally 0.8 mg/mL of warfarin sodium in *Diluent* prepared as follows. Transfer 8–10 Tablets into a suitable volumetric flask, dissolve Tablets in *Diluent* by sonicating for 10 min and shaking for 60 min. Dilute with *Diluent* to volume. Pass through a suitable filter, and discard the first few mL.

Chromatographic system

(See *Chromatography ⟨621⟩, System Suitability*.)

Mode: LC

Detector: UV 280 nm

Column: 4.6-mm × 25-cm; packing L11

Column temperature: 35°

Flow rate: 1.5 mL/min

Injection volume: 200 µL

Run time: NLT 4 times the retention time of warfarin

System suitability

Samples: *Standard solution* and *System suitability solution*

[NOTE—The relative retention times for warfarin and warfarin related compound A are about 1.0 and 1.4, respectively.]

Suitability requirements

Resolution: NLT 2 between warfarin and warfarin related compound A peaks, *System suitability solution*

Relative standard deviation: NMT 5.0%, *Standard solution*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of Alice's ketone in the portion of Tablets taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times (M_{r1}/M_{r2}) \times (1/F) \times 100$$

r_U = peak response of warfarin related compound A from the *Sample solution*

r_S = peak response of warfarin from the *Standard solution*

C_S = concentration of USP Warfarin RS in the *Standard solution* (mg/mL)

C_U = concentration of warfarin sodium in the *Sample solution* (mg/mL)

M_{r1} = molecular weight of warfarin sodium, 330.31

M_{r2} = molecular weight of warfarin, 308.33

F = relative response factor for Alice's ketone, 0.9

[NOTE—Alice's ketone is a sodium salt of warfarin related compound A, 3-(*o*-hydroxyphenyl)-5-phenyl-2-cyclohexen-1-one sodium salt.]

Acceptance criteria: NMT 0.5%

ADDITIONAL REQUIREMENTS

• **PACKAGING AND STORAGE:** Preserve in tight, light-resistant containers. Store at controlled room temperature.

Change to read:

• **USP REFERENCE STANDARDS ⟨11⟩**

USP Warfarin RS

USP Warfarin Related Compound A RS

3-(▲2▲ (ERR 1-Feb-2022) -Hydroxyphenyl)-5-phenyl-2-cyclohexen-1-one.

$C_{18}H_{16}O_2$ ▲264.32▲ (ERR 1-Feb-2022)

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

Topic/Question	Contact	Expert Committee
WARFARIN SODIUM TABLETS	Documentary Standards Support	SM22020 Small Molecules 2

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REFERENCE STANDARD SUPPORT	RS Technical Services RSTECH@usp.org	SM22020 Small Molecules 2

Chromatographic Database Information: Chromatographic Database

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