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Methoxsalen Capsules

DEFINITION

Methoxsalen Capsules contain NLT 90.0% and NMT 110.0% of the labeled amount of methoxsalen ($C_{12}H_8O_4$).

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*.

Change to read:

• **B.** ▲▲**Spectroscopic Identification Tests** ⟨197⟩, *Ultraviolet-Visible Spectroscopy*: **197U**▲ (CN 1-May-2020) ▲ (USP 1-May-2019)

Sample solution: Nominally 4 µg/mL of methoxsalen in alcohol prepared as follows. Place 1 Capsule in 50 mL of alcohol contained in a high-speed glass blender jar, blend thoroughly until the shell is completely dispersed, and dilute a portion with alcohol.

Acceptance criteria: The UV absorption spectrum of the *Sample solution* exhibits maxima and minima at the same wavelengths as those of a similar solution of USP Methoxsalen RS, concomitantly measured.

▲[Note—The UV spectra of the major peaks of the *Sample solution* and the *Standard solution* as obtained in the *Assay* may also be used to meet the *Acceptance criteria*.]▲ (USP 1-May-2019)

ASSAY

Change to read:

• **Procedure**

Mobile phase: Acetonitrile and water (65:35)

Standard stock solution: 0.2 mg/mL of USP Methoxsalen RS in alcohol

Standard solution: 4 µg/mL of USP Methoxsalen RS in *Mobile phase*, from the *Standard stock solution*

Sample stock solution 1 (for hard gelatin Capsules)**:** Nominally equivalent to 0.04 mg/mL of methoxsalen in alcohol prepared as follows. Place NLT 10 Capsules in a high-speed glass blender jar containing 100.0 mL of alcohol, and blend thoroughly. Transfer a portion of the aliquot, nominally equivalent to 2 mg of methoxsalen, from the blender jar into a 50-mL volumetric flask, dilute with alcohol to volume, and filter.

Sample stock solution 2 (for soft gelatin Capsules)**:** Nominally equivalent to 0.04 mg/mL of methoxsalen in alcohol prepared as follows. Place the end of a long-stem glass funnel on a 250-mL volumetric flask, punch a hole at each end of a Capsule with a syringe containing 15 mL of alcohol, and rinse the contents into the flask. Cut the Capsule shell with a scalpel, and wash the inside of the shell with 15 mL of alcohol into the same flask. Repeat these steps for NLT 4 additional Capsules, and collect the rinsings. Wash the funnel, and collect the rinsings in the same flask. Dilute with alcohol to volume, and mix. Transfer a portion of this solution, nominally equivalent to 2 mg of methoxsalen, into a 50-mL volumetric flask. Dilute with alcohol to volume, and filter.

Sample solution: Nominally equivalent to 4 µg/mL of methoxsalen in *Mobile phase*, from *Sample stock solution 1* or *Sample stock solution 2*

Chromatographic system

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

Mode: LC

Detector: UV 254 nm. ▲For *Identification B*, use a diode array detector set at 200–400 nm.▲ (USP 1-May-2019)

Column: 4-mm × 30-cm; packing L1

Flow rate: 1.5 mL/min

Injection volume: 20 µL

System suitability

Sample: *Standard solution*

Suitability requirements

Relative standard deviation: NMT 2.0%

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of methoxsalen ($C_{12}H_8O_4$) in the portion of Capsules taken:

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

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

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

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

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

Acceptance criteria: 90.0%–110.0%

PERFORMANCE TESTS

Change to read:

• **Dissolution** ⟨711⟩

For soft gelatin Capsules

Medium: Water; 900 mL

Apparatus 2: 50 rpm ▲with sinkers, if necessary[1]▲ (USP 1-May-2019)

Time: 45 min

Standard solution: USP Methoxsalen RS in *Medium*. An amount of alcohol NMT 1% of the total volume of the *Standard solution* may be used to bring the Reference Standard into solution before diluting with *Medium*.

Sample solution: Dilute a filtered portion of the solution under test with *Medium* to a concentration similar to that of the *Standard solution*.

Instrumental conditions

Mode: UV

Analytical wavelength: Maximum absorbance at about 300 nm

Analysis

Samples: *Standard solution* and *Sample solution*

▲Calculate the percentage of the labeled amount of methoxsalen ($C_{12}H_8O_4$) dissolved:

$$\text{Result} = (A_U/A_S) \times C_S \times V \times D \times (1/L) \times 100$$

A_U = absorbance of the *Sample solution*

A_S = absorbance of the *Standard solution*

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

V = volume of *Medium*, 900 mL

D = dilution factor for the *Sample solution*, if needed

L = label claim (mg/Capsule)▲ (USP 1-May-2019)

Tolerances: NLT 75% (Q) of the labeled amount of methoxsalen ($C_{12}H_8O_4$) is dissolved.

For hard gelatin Capsules

Medium: Water; 900 mL

Apparatus 1: 150 rpm

Time: 90 min

Sample solution: Filter a portion of the solution under test.

Standard solution: USP Methoxsalen RS in alcohol and diluted with *Medium* to a concentration similar to that of the *Sample solution*

Instrumental conditions

Mode: UV

Analytical wavelength: Maximum absorbance at about 252 nm

Analysis

Samples: *Sample solution* and *Standard solution*

▲Calculate the percentage of the labeled amount of methoxsalen ($C_{12}H_8O_4$) dissolved:

$$\text{Result} = (A_U/A_S) \times C_S \times V \times (1/L) \times 100$$

A_U = absorbance of the *Sample solution*

A_S = absorbance of the *Standard solution*

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

V = volume of *Medium*, 900 mL

L = label claim (mg/Capsule)▲ (USP 1-May-2019)

Tolerances: NLT 75% (Q) of the labeled amount of methoxsalen ($C_{12}H_8O_4$) is dissolved.

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

IMPURITIES

Add the following:

▲• **Organic Impurities**

Solution A: Water

Solution B: Methanol

Mobile phase: See *Table 1*.

Table 1

Time (min)	Solution A (%)	Solution B (%)
0	70	30
35	35	65
40	35	65
42	70	30
50	70	30

Diluent: Methanol and water (7:3)

Standard stock solution: 1.0 mg/mL of USP Methoxsalen RS in methanol

Sensitivity solution: 0.1 µg/mL of USP Methoxsalen RS in *Diluent*, from the *Standard stock solution*

Standard solution: 0.5 µg/mL of USP Methoxsalen RS in *Diluent*, from the *Standard stock solution*

System suitability stock solution A: 0.1 mg/mL of USP Methoxsalen Related Compound A RS in methanol

System suitability stock solution B: 0.1 mg/mL of USP Methoxsalen Related Compound B RS in methanol

System suitability solution: 1.0 µg/mL each of USP Methoxsalen RS, USP Methoxsalen Related Compound A RS, and USP Methoxsalen Related Compound B RS in *Diluent*, from the *Standard stock solution*, *System suitability stock solution A*, and *System suitability stock solution B*, respectively

Sample stock solution: Nominally equivalent to 0.2 mg/mL of methoxsalen in methanol prepared as follows. Transfer the contents of 5 Capsules into a 250-mL volumetric flask. Use methanol to rinse the shells and collect the rinsings in the same volumetric flask. Dilute with methanol to volume.

Sample solution: Nominally equivalent to 0.1 mg/mL of methoxsalen prepared as follows. Transfer 5.0 mL of the *Sample stock solution* into a 10-mL volumetric flask, and dilute with *Diluent* to volume. Pass this solution through a suitable filter of 0.45-µm pore size, discard the first few milliliters, and use the filtrate for analysis.

Chromatographic system

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

Mode: LC

Detector: UV 254 nm

Column: 4.6-mm × 15-cm; 3.5-µm packing L1

Column temperature: 30°

Flow rate: 1.0 mL/min

Injection volume: 20 µL

System suitability

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

Suitability requirements

Resolution: NLT 6.0 between methoxsalen and methoxsalen related compound B; NLT 1.5 between methoxsalen related compound B and methoxsalen related compound A, *System suitability solution*

Relative standard deviation: NMT 10%, *Standard solution*

Signal-to-noise ratio: NLT 10, *Sensitivity solution*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of each impurity in the portion of Capsules taken:

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

r_U = peak area of each impurity from the *Sample solution*

r_S = peak area of methoxsalen from the *Standard solution*

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

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

Acceptance criteria: See *Table 2*.

Table 2

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Methoxsalen	1.00	—
Methoxsalen related compound B[a]	1.24	—
Methoxsalen related compound A[a]	1.25	—
Any individual unspecified impurity	—	0.2
Total impurities	—	0.5▲ (USP 1-May-2019)

[a] This is a process impurity and is listed for identification only. It is controlled in the drug substance. It is not reported for the drug product and should not be included in the total impurities.

ADDITIONAL REQUIREMENTS

Change to read:

• **Packaging and Storage:** Preserve in tight, light-resistant containers. ▲Store at controlled room temperature.▲ (USP 1-May-2019)

• **Labeling:** Label the Capsules to state that Methoxsalen Hard Gelatin Capsules may not be interchangeable with Methoxsalen Soft Gelatin Capsules without retitration of the patient.

Change to read:

• **USP Reference Standards** ⟨11⟩

USP Methoxsalen RS

▲USP Methoxsalen Related Compound A RS

4-Methoxy-7*H*-furo[3,2-*g*]chromen-7-one.

$C_{12}H_8O_4$ 216.19

USP Methoxsalen Related Compound B RS

4,9-Dimethoxy-7*H*-furo[3,2-*g*]chromen-7-one.

$C_{13}H_{10}O_5$ 246.22▲ (USP 1-May-2019)

[1] A suitable sinker is available as catalog number CAPWST-23 from www.qla-llc.com.

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

Topic/Question	Contact	Expert Committee
METHOXSALEN CAPSULES	Documentary Standards Support	SM32020 Small Molecules 3

Chromatographic Database Information: Chromatographic Database

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