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Acitretin Capsules

DEFINITION
Acitretin Capsules contain NLT 90.0% and NMT 110.0% of the labeled amount of acitretin ($C_{21}H_{26}O_3$).

[**Caution**—Acitretin is a teratogen. Great care should be taken when handling to avoid inhalation of dust or contact with skin.]

[Note—Use low-actinic glassware and perform all tests under yellow and subdued light. Make all injections within 1 h of the *Sample solution* preparation.]

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.** The UV spectrum of the major peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay*.

ASSAY
- **Procedure**

Diluent: Methanol and tetrahydrofuran (13:10)

Mobile phase: Methanol, alcohol, glacial acetic acid, and water (74:5:0.5:21)

Standard solution: 0.1 mg/mL of USP Acitretin RS in a mixture of *Diluent* and water (23:2). Dissolve USP Acitretin RS in *Diluent* equivalent to 80% of the final volume, sonicate for 5 min, add water equivalent to 8% of the final volume, and dilute with *Diluent* to volume.

System suitability solution: Transfer 2 mL of the *Standard solution* to a clear 4-mL glass vial. After sealing the vial with a Teflon-lined silicone septum and cap, place the vial on its side in a light chamber, expose it to 400 foot-candles of fluorescent light for 5 min, and then completely wrap the vial with aluminum foil.
[Note—Exposure to the fluorescent light allows for the formation of two degradation products: acitretin related compound A and 6*Z*-isomer ((2*E*,4*E*,6*Z*,8*E*)-9-(4-methoxy-2,3,6-trimethylphenyl)-3,7-dimethylnona-2,4,6,8-tetraenoic acid).]

Sample solution: Nominally 0.1 mg/mL of acitretin in a mixture of *Diluent* and water (23:2). Open NLT 20 Capsules, composite the Capsule fill, and mix well. Transfer the Capsule fill to a volumetric flask, add water equivalent to 8% of the final volume to wet the sample, and sonicate for 5 min. Dilute with *Diluent* to volume, and sonicate for 5 min. Cool to room temperature, pass the suspension through a suitable filter of 0.5-µm pore size, and use the clear filtrate. [Note—Inject the *Sample solution* within 1 h of preparation.]

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

Mode: LC

Detector: UV 365 nm. For *Identification B*, use a diode array detector in the range of 200–400 nm.

Column: 4.6-mm × 15-cm; 5-µm packing L1

Flow rate: 1 mL/min

Injection volume: 25 µL

System suitability

Samples: *Standard solution* and *System suitability solution*
[Note—The relative retention times for acitretin related compound A (2*Z*-isomer), acitretin, and the 6*Z*-isomer are 0.84, 1.0, and 1.09, respectively.]

Suitability requirements

Resolution: NLT 3.0 between acitretin related compound A and acitretin; NLT 1.8 between the 6*Z*-isomer and acitretin, *System suitability solution*

Relative standard deviation: NMT 2.0%, *Standard solution*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of acitretin ($C_{21}H_{26}O_3$) in the portion of Capsules taken:

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

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

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

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

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

Acceptance criteria: 90.0%–110.0%

PERFORMANCE TESTS

• **Dissolution** ⟨711⟩

Test 1

Medium: 3% sodium lauryl sulfate in deaerated water, pH 9.6–10.0; 900 mL

Apparatus 1: 100 rpm

Time: 30 min

Determine the amount of acitretin ($C_{21}H_{26}O_3$) dissolved using the following method.

Standard solution: Transfer about 14 mg of USP Acitretin RS to a 500-mL volumetric flask. Dissolve in 50 mL of alcohol, and dilute with *Medium* to volume.

For Capsules labeled to contain 10 mg: Transfer 20 mL of this solution to a 50-mL volumetric flask, and dilute with *Medium* to volume.

Sample solution: Use portions of the solution under test passed through a suitable filter of 0.45-µm pore size.

Capsule shell solution: Dissolve 6 clean empty-shell Capsules in 900 mL of *Medium*.

Instrumental conditions

Mode: UV

Analytical wavelength: 347 nm

Cell: 2 mm

Blank: *Medium*

Analysis

Samples: *Standard solution*, *Sample solution*, and *Capsule shell solution*

Calculate the percentage of the labeled amount of acitretin ($C_{21}H_{26}O_3$) dissolved:

$$\text{Result} = [(A_U - A_{CS})/A_S] \times (C_S/L) \times V \times 100$$

A_U = absorbance of the *Sample solution*

A_{CS} = Capsule shell correction, calculated as shown below

A_S = absorbance of the *Standard solution*

C_S = concentration of the appropriate *Standard solution* (mg/mL)

L = label claim (mg/Capsule)

V = volume of *Medium*, 900 mL

The Capsule shell correction, A_{CS}, is calculated:

$$A_{CS} = A_{CSS}/N$$

A_{CSS} = absorbance of the *Capsule shell solution*

N = number of Capsule shells used to prepare the *Capsule shell solution*

Tolerances: NLT 85% (*Q*) of the labeled amount of acitretin ($C_{21}H_{26}O_3$) is dissolved.

Test 2: If the product complies with this test, the labeling indicates that the product meets USP *Dissolution Test 2*.

Tier 1

Medium: 3% sodium lauryl sulfate in deaerated water, pH 9.6–10.0 (adjusted with 1 N sodium hydroxide); 900 mL

Apparatus 1: 100 rpm

Time: 30 min

Tier 2

Medium A: Prepare a solution containing pancreatin with NMT 2000 USP Units/L of protease activity in deaerated water, pH 8.0 (adjusted with 1% sodium hydroxide); 450 mL. Use immediately.

Medium B: 6% sodium lauryl sulfate in deaerated water, pH 10.5 (adjusted with 1% sodium hydroxide); 450 mL

Apparatus 1: 100 rpm

Time: 15 min, *Medium A*; 15 min, *Medium A* with the addition of *Medium B*

Determine the amount of acitretin ($C_{21}H_{26}O_3$) dissolved using the following method.

Mobile phase: Methanol, water, and glacial acetic acid (750:250:1)

Standard stock solution: 280 µg/mL of USP Acitretin RS in absolute alcohol. Use sonication to dissolve.

Standard solution: 20 µg/mL of USP Acitretin RS in *Medium* under *Tier 1*, from *Standard stock solution*

Sample solution: Pass a portion of the solution under test through a suitable glass filter with 1-µm pore size, discard the first few mL, and use the filtrate for analysis.

Dissolution procedure: Perform the test using the conditions under *Tier 1*. In the presence of cross-linking repeat the test with new Capsules using the conditions under *Tier 2* as follows. After 15 min, stop the dissolution bath and timer (do not lift the baskets), and add 450 mL of *Medium B* pre-equilibrated at 37 ± 0.5°. Restart the timer and bath, and after 5 min check the pH of the medium and adjust with 1% sodium hydroxide to a range of 9.6–10.0. Continue dissolution for an additional 10 min.

Chromatographic system

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

Mode: LC

Detector: 360 nm

Columns

Guard: 4-mm × 1-cm; 5-µm packing L1

Analytical: 4.6-mm × 5-cm; 5-µm packing L1

Temperatures

Autosampler: 40°

Column: 35°

Flow rate: 2.0 mL/min

Injection volume: 10 µL

System suitability

Sample: *Standard solution*

Suitability requirements

Tailing factor: NMT 2.0

Relative standard deviation: NMT 2.0%

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of acitretin ($C_{21}H_{26}O_3$) dissolved:

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

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

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

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

L = label claim (mg/Capsule)

V = volume of *Medium*, 900 mL

Tolerances: NLT 85% (*Q*) of the labeled amount of acitretin ($C_{21}H_{26}O_3$) is dissolved.

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

IMPURITIES

• **Organic Impurities: Limit of Degradation Products**

Diluent, Mobile phase, System suitability solution, Sample solution, Chromatographic system, and **System suitability:** Proceed as directed in the *Assay*.

Analysis

Sample: *Sample solution*

Calculate the percentage of each degradation product in the portion of Capsules taken:

$$\text{Result} = (r_U/r_T) \times 100$$

r_U = peak response of each individual impurity from the *Sample solution*

r_T = sum of the responses of all the peaks from the *Sample solution*

Acceptance criteria: See *Table 1*.

Table 1

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Acitretin related compound A (2*Z*-isomer)[a]	0.84	0.5

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Acitretin	1.0	—
Any unspecified impurity	—	0.4
Total unspecified impurities	—	0.8

[a] (2*Z*,4*E*,6*E*,8*E*)-9-(4-Methoxy-2,3,6-trimethylphenyl)-3,7-dimethylnona-2,4,6,8-tetraenoic acid ($C_{21}H_{26}O_3$ 326.43).

ADDITIONAL REQUIREMENTS

- **Packaging and Storage:** Preserve in well-closed, light-resistant containers.
- **Labeling:** When more than one *Dissolution* test is given, the labeling states the test used only if *Test 1* is not used.
- **USP Reference Standards** ⟨11⟩
  USP Acitretin RS

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

Topic/Question	Contact	Expert Committee
ACITRETIN CAPSULES	Documentary Standards Support	SM32020 Small Molecules 3
REFERENCE STANDARD SUPPORT	RS Technical Services RSTECH@usp.org	SM32020 Small Molecules 3

Chromatographic Database Information: Chromatographic Database

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