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Isotretinoin Capsules

DEFINITION

Isotretinoin Capsules contain NLT 90.0% and NMT 110.0% of the labeled amount of isotretinoin (C₂₀H₂₈O₂).

[CAUTION—Isotretinoin is teratogenic. Avoid inhalation and skin contact.]

Avoid exposure to strong light, and use low-actinic glassware in the performance of the following procedures.

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

Change to read:

• **PROCEDURE**

Protect the ▲solutions containing isotretinoin ▲ (IRA 1-Mar-2023) from direct light.

Solution A: 0.5% [acetic acid](#) in [methanol](#)

Solution B: 0.5% [acetic acid](#) in [water](#)

Mobile phase: *Solution A* and *Solution B* (71:29)

▲**Procedure 1** ▲ (IRA 1-Mar-2023)

Diluent: Heat [0.1 N sodium hydroxide](#) to about 60°–70°. Cool to room temperature, purge with helium or nitrogen, and store in a plastic container.

System suitability solution: 0.04 mg/mL of [USP Isotretinoin RS](#) and 0.02 mg/mL of [USP Tretinoin RS](#) in *Diluent*

Standard solution: 0.04 mg/mL of [USP Isotretinoin RS](#) in *Diluent*

Sample stock solution: Nominally 0.4 mg/mL of isotretinoin in *Diluent*, prepared as follows. Transfer Capsules (NLT 10) to a suitable volumetric flask. Add *Diluent* to the volumetric flask to fill about 50% of the volume, sonicate for 1 h with occasional shaking to disperse all of the contents, and dilute with *Diluent* to volume.

Sample solution: Nominally 0.04 mg/mL of isotretinoin in *Diluent* from the *Sample stock solution*. Pass the solution through a suitable membrane filter of 0.45-µm or finer pore size.

▲**Procedure 2**

Procedure 2 may be more suitable for formulations that do not contain surfactant.

Protect solutions containing isotretinoin from light and store at 2°–8°.

Solution C : 0.28 mg/mL of [alpha tocopherol](#) in [methanol](#). [NOTE—[Alpha tocopherol](#) is used to prevent the oxidation of isotretinoin in the *Standard solutions*.]

Standard stock solution A: About 0.25 mg/mL of [USP Isotretinoin RS](#) prepared as follows. Transfer about 25 mg of [USP Isotretinoin RS](#) to a 100-mL volumetric flask. Add 1.0 mL of *Solution C* and about 20 mL of [tetrahydrofuran](#) to the same flask. Shake and swirl to dissolve. Dilute with [methanol](#) to volume.

Standard stock solution B: 0.2 mg/mL of [USP Tretinoin RS](#) in [methanol](#). Sonicate to dissolve.

System suitability solution: 0.04 mg/mL of [USP Isotretinoin RS](#) from *Standard stock solution A* and 0.02 mg/mL of [USP Tretinoin RS](#) from *Standard stock solution B* in [methanol](#)

Standard solution: 0.005 mg/mL of [USP Isotretinoin RS](#) from *Standard stock solution A* in [methanol](#).

Sample stock solution: Follow the steps given below and the information provided in the [Table 1](#) to prepare the *Sample stock solution*.

Table 1

Capsule Label Claim (mg)	No. of Capsules	Volume of Methylene Chloride or Isopropyl Alcohol (mL)	Size of Volumetric Flask (mL)	Final Concentration (µg/mL)
10	20	30	200	1000
20	10	30	200	1000

Capsule Label Claim (mg)	No. of Capsules	Volume of Methylene Chloride or Isopropyl Alcohol (mL)	Size of Volumetric Flask (mL)	Final Concentration (µg/mL)
30	17	35	250	2040
40	10	30	200	2000

1. Pierce one end of each capsule with an awl, cut the capsule and transfer the capsule contents and shells into a 250-mL separating funnel.
2. Rinse the utensils used with the specified volume of [methylene chloride](#) into the separating funnel. Swirl and shake vigorously, and transfer the liquid into the volumetric flask with the specified size.
3. Add the same volume of [methylene chloride](#) into the separating funnel, swirl and shake vigorously, and transfer the liquid into the same volumetric flask.
4. Rinse the separating funnel several times with the specified volume of [isopropyl alcohol](#), transfer each rinsing into the flask, and dilute with [isopropyl alcohol](#) to volume.

Sample solution : Nominally 0.005 mg/mL of isotretinoin from the *Sample stock solution* in [methanol](#). Place the sample flask in a freezer for at least 1 hr to aid the solidification of the fat. Upon removing the flask from the freezer, immediately pass the supernatant through a suitable filter of 0.2-µm pore size, discarding the first few milliliters of filtrate.▲ (IRA 1-Mar-2023)

Chromatographic system

(See [Chromatography \(621\)](#), [System Suitability](#).)

Mode: LC

Detector: UV 353 nm. For *Identification B*, use a diode array detector in the range of 230–400 nm.

Column: 4.6-mm × 25-cm; ▲10-µm▲ (IRA 1-Mar-2023) packing [L1](#)

▲**Autosampler temperature:** 5° (for *Procedure 2* only)▲ (IRA 1-Mar-2023)

Flow rate: 1.5 mL/min

Injection volume: 20 µL

▲**Run time:** NLT 1.5 times the retention time of isotretinoin▲ (IRA 1-Mar-2023)

System suitability

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

[NOTE—The relative retention times for isotretinoin and tretinoin are 1.0 and 1.3, respectively.]

Suitability requirements

Resolution: NLT 2.0 between isotretinoin and tretinoin▲▲ (IRA 1-Mar-2023), *System suitability solution*

Tailing factor: NMT 2.0 for isotretinoin▲▲ (IRA 1-Mar-2023), *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 isotretinoin ($C_{20}H_{28}O_2$) in the portion of Capsules taken:

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

r_U = peak area▲ of isotretinoin▲ (IRA 1-Mar-2023) from the *Sample solution*

r_S = peak area▲ of isotretinoin▲ (IRA 1-Mar-2023) from the *Standard solution*

C_S = concentration of [USP Isotretinoin RS](#) in the *Standard solution* (mg/mL)

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

Acceptance criteria: 90.0%–110.0%

PERFORMANCE TESTS

Change to read:

- [DISSOLUTION \(711\)](#).

Protect the solutions containing isotretinoin from light.

Test 1

Medium

Stage 1: Simulated gastric fluid with pepsin, prepared fresh and purged with nitrogen

Stage 2: 0.13 N [sodium hydroxide](#) (5 g/L of [sodium hydroxide](#) in [water](#)). Prepare fresh, and purge with nitrogen.

Apparatus (see [Disintegration \(701\)](#)): No disks; the apparatus is adjusted so that the bottom of the basket-rack assembly descends to 1.0 ± 0.1 cm from the inside bottom surface of the vessel on the downward stroke; the 10-mesh stainless steel cloth in the basket-rack assembly is replaced with a 40-mesh stainless steel cloth; a 10-mesh stainless-steel cloth is fitted to the top of the basket-rack assembly.

Time: 60 min

Standard solution: Transfer 10 mg of [USP Isotretinoin RS](#) to a 200-mL volumetric flask. Add 25.0 mL of *Stage 1 Medium* and about 150 mL of *Stage 2 Medium*, sonicate until completely dissolved (about 20 min), and dilute with *Stage 2 Medium* to volume. Pass 20 mL of this solution through a suitable filter, discarding the first 5 mL. Dilute 5.0 mL of the filtrate with *Stage 2 Medium* to 50 mL.

Sample solutions: Perform a dissolution test on each of 6 Capsules. Place 1 Capsule in one of the tubes in each of six basket-rack assemblies. Place each basket in a 1-L beaker containing 100 mL of *Stage 1 Medium* in a bath having a temperature of $37.0 \pm 0.5^\circ$. Allow to stand for 30 min. Carefully add 800 mL of *Stage 2 Medium* to each beaker. With the disintegration apparatus operating, connect each basket-rack assembly to the drive rod in a timed sequence. After 60 min, withdraw 20 mL of *Medium* (*Stage 1* and *Stage 2*), and immediately pass the solution through a suitable membrane filter of 0.45- μ m pore size. Discard the first 5 mL, and collect the solution in argon-charged glassware. Dilute, if necessary, with *Stage 2 Medium* to obtain a theoretical concentration of 5.5 μ g/mL of isotretinoin, assuming complete dissolution, based on the label claim.

Capsule shell correction solution: Empty the contents of 3 Capsules. Wash the Capsule shells in several 20-mL aliquots of [chloroform](#). Allow the Capsule shells to air dry. Place the Capsule shells in a 1-L flask containing 100 mL of *Stage 1 Medium* and 800 mL of *Stage 2 Medium*. Allow the flask to stand for about 1 h in a bath with a temperature of $37.0 \pm 0.5^\circ$, stirring occasionally. Filter, and dilute as described for the *Sample solutions*.

Analysis

Detector: UV 343 nm

Blank: *Medium* (*Stage 1* and *Stage 2*)

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

Determine the amount of isotretinoin ($C_{20}H_{28}O_2$) dissolved, correcting for the Capsule shell absorbance.

Calculate the percentage of the labeled amount of isotretinoin ($C_{20}H_{28}O_2$) dissolved:

$$\text{Result} = [(A_U - A_C)/A_S] \times (C_S/L) \times D \times 100$$

A_U = absorbance of the *Sample solutions*

A_C = absorbance of the *Capsule shell correction solution*

A_S = absorbance of the *Standard solution*

C_S = concentration of [USP Isotretinoin RS](#) in the *Standard solution* (mg/mL)

L = label claim (mg/Capsule)

D = dilution factor for the *Sample solutions*

Tolerances: NLT 80% (Q) of the labeled amount of isotretinoin ($C_{20}H_{28}O_2$) is dissolved.

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

Medium: 0.05 M phosphate buffer, pH 7.8, containing 0.5% (w/v) solid [N,N-dimethyldodecylamine N-oxide](#); 900 mL

Apparatus 1: 20-mesh basket; 100 rpm

Time: 90 min

Buffer solution: 3.4 mg/mL of [monobasic potassium phosphate](#). Adjust with [phosphoric acid](#) to a pH of 2.10 ± 0.05 .

Mobile phase: [Methanol](#) and *Buffer solution* (81:19)

Standard solution: Transfer about 44 mg of [USP Isotretinoin RS](#) to a 100-mL volumetric flask. Add 15 mL of [1-propanol](#), and sonicate for about 15 min. Add 50 mL of *Medium*, and sonicate for 10 min. Dilute with *Medium* to volume. Transfer 5.0 mL of the resulting solution to a 100-mL volumetric flask, and dilute with *Medium* to volume. Dilute this solution with *Medium* to obtain a final concentration of about (L/1000) mg/mL, where L is the label claim, in mg/Capsule.

Sample solution: Pass a portion of the solution under test through a suitable membrane filter of 0.45- μ m pore size.

Chromatographic system

(See [Chromatography \(621\)](#), *System Suitability*.)

Mode: LC

Detector: UV 358 nm

Column: 4.6-mm $\times$ 5-cm; 5- μ m packing [L1](#)

Flow rate: 2.0 mL/min

Injection volume: 10 μ L

▲**Run time:** NLT 1.5 times the retention time of isotretinoin▲ (IRA 1-Mar-2023)

System suitability

Sample: *Standard solution*

Suitability requirements

Tailing factor: NMT 2.0