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Anagrelide Capsules

DEFINITION
Anagrelide Capsules contain NLT 90.0% and NMT 110.0% of the labeled amount of anagrelide ($C_{10}H_7Cl_2N_3O$).

IDENTIFICATION
• **A.** The UV absorption spectrum of the major peak of the *Sample solution* exhibits maxima and minima at the same wavelengths as those of the corresponding peak of the *Standard solution*, as obtained in the *Assay*.
• **B.** The retention time of the major peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay*.

ASSAY
• **Procedure**

Solution A: 1.0 g/L of sodium hexanesulfonate. Add 1.0 mL of phosphoric acid and filter.

Mobile phase: Acetonitrile and *Solution A* (7:13)

Diluent: Acetonitrile and water (1:1)

Standard stock solution: 0.25 mg/mL of USP Anagrelide Hydrochloride RS in acetonitrile. Initially add acetonitrile (about 80% of the volume of the flask) and a small quantity of 2 N hydrochloric acid (about 0.2 mL for every 100 mL of the final volume). Sonicate to dissolve, and dilute with acetonitrile to volume.

Standard solution: 0.01 mg/mL of anagrelide free base in *Diluent* from *Standard stock solution*

Sample solution: Nominally 0.01 mg/mL of anagrelide free base prepared from the contents of NLT 20 Capsules. Add *Diluent* (80% of the volume of the flask), sonicate for 10 min, and stir for 15 min. Further dilute with *Diluent* to volume, centrifuge for 15 min at 4000 rpm, and use the supernatant for analysis.

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

Mode: LC

Detector: UV 254 nm. For *Identification A*, use a diode array detector in the range of 200–400 nm.

Column: 4.6-mm × 15-cm; 4-µm packing L11

Column temperature: 60°

Flow rate: 1.0 mL/min

Injection volume: 20 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 anagrelide ($C_{10}H_7Cl_2N_3O$) in the portion of Capsules taken:

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

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

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

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

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

Acceptance criteria: 90.0%–110.0%

PERFORMANCE TESTS
Change to read:
• **Dissolution ⟨711⟩**

Medium: 0.1 N hydrochloric acid; 900 mL

Apparatus 1: 100 rpm

Time: 15 min

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

Standard solution: Transfer about 30.32 mg of USP Anagrelide Hydrochloride RS, equivalent to 25.00 mg of anagrelide, to a 100-mL volumetric flask. Add about 80 mL of acetonitrile and 3 drops of 2 N hydrochloric acid. Sonicate until dissolved. Dilute with acetonitrile 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 filter of 0.45-µm pore size.

Chromatographic system

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

Mode: LC

Detector: UV 274 nm

Column: 4.6-mm × 15-cm; 5-µm packing L7

Sample cooler temperature: 5°

Flow rate: 1.0 mL/min

Injection volume: 20 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 anagrelide dissolved:

$$\text{Result} = (r_U/r_S) \times C_S \text{▲ (ERR 1-Oct-2019)} \times (M_{r1}/M_{r2}) \times (V/L) \times 100$$

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

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

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

▲ (ERR 1-Oct-2019)

M_{r1} = molecular weight of anagrelide, 256.09

M_{r2} = molecular weight of anagrelide hydrochloride, 292.55

V = volume of *Medium*, 900 mL

L = label claim (mg/Capsule)

Tolerances: NLT 80% (*Q*) of the labeled amount of anagrelide is dissolved.

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

IMPURITIES

• **Organic Impurities**

Buffer: 6.8 g/L of monobasic potassium phosphate. Adjust with diluted phosphoric acid to a pH of 3.50 ± 0.05. Mix well and filter.

Mobile phase: Acetonitrile and *Buffer* (27:73)

Diluent: Acetonitrile and water (7:13)

Related compound A stock solution: 10 µg/mL of USP Anagrelide Related Compound A RS in *Diluent*

Related compound C stock solution: 10 µg/mL of USP Anagrelide Related Compound C RS in *Diluent*

System suitability solution: 0.2 µg/mL each of USP Anagrelide Related Compound A RS and USP Anagrelide Related Compound C RS and 0.02 mg/mL of USP Anagrelide Hydrochloride RS prepared as follows. Initially dissolve USP Anagrelide Hydrochloride RS in *Diluent* (about 80% of the volume of the flask), sonicate for 10 min, and stir for 15 min. Add appropriate quantities of *Related compound A stock solution* and *Related compound C stock solution*, and dilute with *Diluent* to volume.

Standard stock solution: Prepare as directed in the *Assay*.

Standard solution: 0.10 µg/mL of anagrelide free base in *Diluent* from *Standard stock solution*

Sample solution: Nominally 0.02 mg/mL of anagrelide free base from NLT 20 Capsules. Initially add *Diluent* to about 80% of the volume of the flask, sonicate for 10 min, stir for about 15 min, and dilute with *Diluent* to volume. Centrifuge the solution at about 4000 rpm for 15 min, and use the supernatant for analysis.

Chromatographic system

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

Mode: LC

Detector: UV 254 nm

Column: 4.6-mm × 15-cm; 4-µm packing L11

Column temperature: 45°

Flow rate: 1 mL/min

Injection volume: 30 µL

System suitability

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

Suitability requirements

Resolution: NLT 2.0 between anagrelide hydrochloride and anagrelide related compound C, and between anagrelide hydrochloride and anagrelide related compound A, *System suitability solution*

Tailing factor: NMT 2.0, *Standard solution*

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

Analysis

Samples: *Standard solution* and *Sample solution*

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

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

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

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

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

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

F = relative response factor (see *Table 1*)

Acceptance criteria: See *Table 1*.

Table 1

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Anagrelide related compound A[a]	0.86	—	—
Anagrelide hydrochloride	1.0	—	—
Anagrelide related compound B[b]	0.3	0.34	1.0
Anagrelide related compound C[a]	1.15	—	—
Anagrelide trichloro derivative[c]	1.8–2.3	1.0	0.15
Any other individual impurity	—	—	0.2
Total impurities	—	—	1.5

[a] This is a process-related impurity and controlled in the drug substance.

[b] [2-Amino-5,6-dichloroquinazoline-3(4*H*)-yl]acetic acid.

[c] 6,7,8-Trichloro-3,5-dihydroimidazo[2,1-*b*]quinazolin-2(1*H*)-one.

ADDITIONAL REQUIREMENTS

- **Packaging and Storage:** Preserve in tight containers, protected from light. Store at controlled room temperature.
- **USP Reference Standards** ⟨11⟩

USP Anagrelide Hydrochloride RS

USP Anagrelide Related Compound A RS

Ethyl 2-(6-amino-2,3-dichlorobenzylamino)acetate.

$C_{11}H_{14}Cl_2N_2O_2$ 277.15

USP Anagrelide Related Compound C RS

Ethyl 2-(5,6-dichloro-2-imino-1,2-dihydroquinazolin-3(4*H*)-yl)acetate hydrobromide.
$C_{12}H_{13}Cl_2N_3O_2 \cdot HBr$ 383.07

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

Topic/Question	Contact	Expert Committee
ANAGRELIDE CAPSULES	Documentary Standards Support	SM22020 Small Molecules 2
REFERENCE STANDARD SUPPORT	RS Technical Services RSTECH@usp.org	SM22020 Small Molecules 2

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