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Digoxin Tablets

DEFINITION
Digoxin Tablets contain NLT 90.0% and NMT 105.0% of the labeled amount of digoxin ($C_{41}H_{64}O_{14}$).

IDENTIFICATION

• **A. Thin-Layer Chromatographic Identification Test ⟨201⟩**

Diluent: Dehydrated alcohol

Standard solution: 0.25 mg/mL of USP Digoxin RS in *Diluent*

Sample solution: Transfer a quantity of finely powdered Tablets, equivalent to 0.5 mg of digoxin, into a 10-mL centrifuge tube. Add 2 mL of *Diluent*, sonicate for 10–15 min, and centrifuge. Decant and use the supernatant.

Chromatographic system

(See *Chromatography ⟨621⟩, Thin-Layer Chromatography*.)

Mode: TLC

Adsorbent: 0.25-mm layer of chromatographic silica gel mixture to which octadecylsilane (C18) is permanently bonded

Application volume: 10 µL

Developing solvent system: Methanol and water (7:3)

Spray reagent: Mix 10 mL of a freshly prepared solution of chloramine T (3 in 100) and 40 mL of a 1 in 4 solution of trichloroacetic acid in dehydrated alcohol. [Note—Mix before use.]

Analysis

Samples: *Standard solution* and *Sample solution*

Apply the *Samples* on a line parallel to and about 2.5 cm from the bottom edge of a reversed-phase thin-layer chromatographic plate. Allow the spots to dry, and place the plates in a developing chamber. Develop the chromatogram until the solvent front has moved about 15 cm above the line of application. Remove the plate, and allow the solvent to evaporate. Spray the plate with *Spray reagent*, and heat in an oven at 110° for 10 min. Examine the plate under long-wavelength UV light.

Acceptance criteria: The R_F value of the principal spot of the *Sample solution* corresponds to that of the *Standard solution*.

• **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

Change to read:

• **Procedure**

Mobile phase: Acetonitrile and water (13:37)

System suitability solution: 40 µg/mL each of USP Digoxin RS and digoxigenin in diluted alcohol

Standard solution: 40 µg/mL of USP Digoxin RS in diluted alcohol. [Note—Use a sonic bath to aid dissolution.]

Sample solution: Weigh and finely powder NLT 20 Tablets. Transfer a portion of the powder, equivalent to 1 mg of digoxin, to a glass-stoppered, 50-mL conical flask. Add 25.0 mL of diluted alcohol with swirling, sonicate for 30 min, and cool. Pass a portion of this solution through a 0.8-µm pore size membrane filter, discarding the first 10 mL of the filtrate.

Chromatographic system

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

Mode: LC

Detector: UV 218 nm

Column: 4.6-mm × 25-cm; 5-µm packing L1

Temperature: 25°

Flow rate: 2 mL/min

Injection volume: 50 µL

System suitability

Sample: *System suitability solution*

Suitability requirements

Resolution: NLT 4.0 between digoxin and digoxigenin

Column efficiency: NLT 1200 theoretical plates

Tailing factor: NMT 2.0

Relative standard deviation: NMT 2.0%

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of digoxin ($C_{41}H_{64}O_{14}$) in the portion of Tablets taken:

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

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

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

C_S = concentration of USP Digoxin RS in the *Standard solution* (µg/mL)

C_U = nominal concentration of ▲digoxin▲ (ERR 1-Oct-2023) in the *Sample solution* (µg/mL)

Acceptance criteria: 90.0%–105.0%

PERFORMANCE TESTS

• **Dissolution** ⟨711⟩

Test 1

[Note—Throughout this procedure, use scrupulously clean glassware, rinsed successively with hydrochloric acid, water, and alcohol, and carefully dried. Take precautions to prevent contamination from fluorescent particles and from metal and rubber surfaces.]

Medium: 0.1 N hydrochloric acid; 500 mL

[Note—Use the same batch of *Medium* throughout the test.]

Apparatus 1: 120 rpm

Time: 60 min

Solution A: 2 mg/mL of ascorbic acid in methanol

Solution B: On the day of use, dilute 2.0 mL of recently assayed 30% hydrogen peroxide with methanol to 100 mL. Store in a refrigerator. Just before use, dilute 2.0 mL of this solution with methanol to 100 mL.

Standard solutions: Transfer 25 mg of USP Digoxin RS into a 500-mL volumetric flask. Dissolve in a minimum amount of alcohol, then add diluted alcohol (4 in 5) to volume. Dilute 10.0 mL of this solution with diluted alcohol (4 in 5) to 100.0 mL. Just before use, dilute suitable aliquots of the resulting solution with *Medium* to 50.0 mL to prepare *Standard solutions* equivalent to 20%, 40%, 60%, 80%, and 100%, respectively, of the labeled amount of digoxin in 500 mL.

Sample solution: Promptly after withdrawal, pass a portion of the solution under test through a filter having a 0.8-µm or finer pore size, discarding the first 10 mL of the filtrate.

Analysis: Transfer to individual glass-stoppered flasks duplicate 1.0-mL portions of the *Sample solution*, 1.0-mL portions of each of the *Standard solutions*, and 1.0 mL of the *Medium* to provide a blank. Begin with the *Standard solutions*, and keep all flasks in the same sequence throughout, so that the elapsed time from addition of reagents to reading of fluorescence is the same for each flask in the set. Treating one flask at a time, add the following three reagents, in the order named, in as rapid a sequence as possible, swirling after each addition: 1.0 mL of *Solution A*, 5.0 mL of hydrochloric acid, and 1.0 mL of *Solution B*. Insert the stoppers in the flasks. After 2 h, measure the fluorescence at about 485 nm, the excitation wavelength being about 372 nm. To check the stability of the fluorometer, repeat the measurement of fluorescence on one or more treated *Standard solutions*. Correct each reading for the blank, and plot a standard curve of fluorescence versus percentage dissolution.

Determine the percentage dissolution of digoxin in the *Sample solution* by reading from the standard graph.

Tolerances: NLT 80% (*Q*) of the labeled amount of $C_{41}H_{64}O_{14}$ is dissolved. The requirement is met if the quantities dissolved from the Tablets tested conform to *Table 1* instead of the table shown under *Dissolution* ⟨711⟩.

Table 1

Stage	Number Tested	Acceptance Criteria
S_1	6	Each unit is NLT Q + 5%.
S_2	6	Average of 12 units (S_1 + S_2) is equal to or greater than Q, and no unit is less than Q − 5%.

Test 2

[Note—If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 2*.]

Medium: Water, deaerated, 500 mL

Apparatus 1: 120 rpm

Time: 20 min

Solution A: Mix 890 mL of water with 110 mL of acetonitrile.

Solution B: Mix 100 mL of water with 900 mL of acetonitrile.

Mobile phase: Mix 650 mL of *Solution A* and 350 mL of *Solution B*.

Standard stock solution: Transfer 25 mg of USP Digoxin RS to a 200-mL volumetric flask and dissolve with 10 mL of methanol. Fill up to the volume with *Medium*.

Standard solution: Dilute the *Standard stock solution* with *Medium* in order to obtain a final concentration of *L*/500 mg/mL, where *L* is the product label claim in milligrams.

Sample solution: Pass 10 mL of the solution under test through a suitable polyvinylidene fluoride (PVDF) filter of 0.45-µm pore size, discarding the first 4 mL. Dilute with *Medium*.

Chromatographic system

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

Mode: LC

Detector: UV 220 nm

Column: 3.0-mm × 5-cm; 3.5-µm packing L11

Temperatures

Column: 40°

Autosampler: 5°

Injection volume: 500 µL

Flow rate: See *Table 2*.

Table 2

Time (min)	Flow Rate (mL/min)
0.0	0.6
2.5	0.6
3.0	2.0
6.0	2.0

System suitability

Sample: *Standard solution*

Suitability requirements

Tailing factor: NMT 2.0

Relative standard deviation: NMT 5.0%

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentages of the labeled amount of digoxin ($C_{41}H_{64}O_{14}$) dissolved:

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

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

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

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

D = dilution factor for the *Sample solution*

V = volume of *Medium*, 500 mL

L = label claim (mg)

Tolerances: NLT 80% (*Q*) of the labeled amount of digoxin ($C_{41}H_{64}O_{14}$) is dissolved. The requirement is met if the quantities dissolved from the Tablets tested conform to *Table 3* instead of the table shown under *Dissolution ⟨711⟩*.

Table 3

Stage	Number Tested	Acceptance Criteria
S_1	6	NLT 80% (*Q*) of the labeled amount of digoxin

Stage	Number Tested	Acceptance Criteria
S_2	12	Average of 12 units (S_1 + S_2) is equal to or greater than Q, and no unit is less than Q − 5%.

• **Uniformity of dosage units ⟨905⟩:** Meet the requirements

ADDITIONAL REQUIREMENTS

• **Packaging and Storage:** Preserve in tight containers.

• **Labeling:** The labeling states the *Dissolution* test used only if *Test 1* is not used.

• **USP Reference standards ⟨11⟩**
USP Digoxin RS

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

Topic/Question	Contact	Expert Committee
DIGOXIN TABLETS	Nam-Cheol Kim Scientific Liaison	BDSHM2020 Botanical Dietary Supplements and Herbal Medicines

Chromatographic Database Information: Chromatographic Database

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