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Hydrocodone Bitartrate and Homatropine Methylbromide Tablets

DEFINITION

Hydrocodone Bitartrate and Homatropine Methylbromide Tablets contain NLT 90.0% and NMT 110.0% of the labeled amounts of hydrocodone bitartrate disesquihydrate ($C_{18}H_{21}NO_3 \cdot C_4H_6O_6 \cdot 2½H_2O$) and homatropine methylbromide ($C_{17}H_{24}BrNO_3$).

[NOTE—Use of silanized autosampler vials such as dimethyldichlorosilane vials[1] is required for *Dissolution Test 1* and *Test 2*, the *Limit* tests, and the *Assay* to prevent drug degradation.]

IDENTIFICATION

• **A.** The UV absorption spectra of the hydrocodone bitartrate and homatropine methylbromide peaks of the *Sample solution* and those of the *Standard solution* exhibit maxima and minima at the same wavelengths, as obtained in the *Assay*.

• **B.** The retention times of the hydrocodone bitartrate and homatropine methylbromide peaks of the *Sample solution* correspond to those of the *Standard solution*, as obtained in the *Assay*.

ASSAY

Change to read:

• **PROCEDURE**

Buffer: 0.005 M dibasic potassium phosphate. Adjust with phosphoric acid to a pH of 6.4 ± ▲0.1▲ (ERR 1-Jul-2022).

Mobile phase: Acetonitrile and *Buffer* (30:170)

Standard solution: 0.2 mg/mL of USP Hydrocodone Bitartrate RS and 0.06 mg/mL of USP Homatropine Methylbromide RS in *Mobile phase*

Sample solution: Nominally 0.2 mg/mL of hydrocodone bitartrate and 0.06 mg/mL of homatropine methylbromide prepared as follows. Transfer a portion of fine powder from NLT 20 Tablets to a suitable volumetric flask. Add 60% of the final volume of *Mobile phase*, sonicate for 15 min, and then shake with a wrist-action shaker for an additional 15 min. Dilute with *Mobile phase* to volume. Pass the solution through a suitable filter of 0.45-µm pore size.

Chromatographic system

Mode: LC

Detectors

Assay: UV 230 nm

Identification test A: Diode array, UV 200–400 nm

Column: 4.6-mm × 25-cm; 5-µm packing L7

Flow rate: 1.5 mL/min

Injection volume: 10 µL

System suitability

Sample: *Standard solution*

[NOTE—The relative retention times for homatropine methylbromide and hydrocodone bitartrate are about 0.44 and 1.0, respectively.]

Suitability requirements

Resolution: NLT 2.5 between hydrocodone bitartrate and homatropine methylbromide

Relative standard deviation: NMT 3.0% for each analyte

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of homatropine methylbromide ($C_{17}H_{24}BrNO_3$) in the portion of Tablets taken:

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

r_U = peak response of homatropine methylbromide from the *Sample solution*

r_S = peak response of homatropine methylbromide from the *Standard solution*

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

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

Calculate the percentage of the labeled amount of hydrocodone bitartrate disesquihydrate ($C_{18}H_{21}NO_3 \cdot C_4H_6O_6 \cdot 2½H_2O$) in the portion of Tablets taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times (M_{r1}/M_{r2}) \times 100$$

r_U = peak response of hydrocodone bitartrate from the *Sample solution*

r_S = peak response of hydrocodone bitartrate from the *Standard solution*

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

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

M_{r1} = molecular weight of hydrocodone bitartrate disesquihydrate, 494.49

M_{r2} = molecular weight of anhydrous hydrocodone bitartrate, 449.46

Acceptance criteria: 90.0%–110.0%

PERFORMANCE TESTS

• **Dissolution** ⟨711⟩

Test 1

Medium: Water; 900 mL, deaerated

Apparatus 2: 50 rpm

Time: 30 min

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

Standard solution: 0.0055 mg/mL of USP Hydrocodone Bitartrate RS and 0.00165 mg/mL of USP Homatropine Methylbromide RS in *Medium*

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

Chromatographic system: Proceed as directed in the *Assay*, with the following exception.

Injection volume: 250 µL

System suitability

Sample: *Standard solution*

Suitability requirements

Resolution: NLT 13 between homatropine methylbromide and hydrocodone bitartrate

Relative standard deviation: NMT 3.0% for each analyte

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amounts of hydrocodone bitartrate disesquihydrate ($C_{18}H_{21}NO_3 \cdot C_4H_6O_6 \cdot 2½H_2O$) and homatropine methylbromide ($C_{17}H_{24}BrNO_3$) dissolved:

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

r_U = peak area of hydrocodone bitartrate or homatropine methylbromide from the *Sample solution*

r_S = peak area of hydrocodone bitartrate or homatropine methylbromide from the *Standard solution*

C_S = concentration of USP Hydrocodone Bitartrate RS or USP Homatropine Methylbromide RS in the *Standard solution* (mg/mL)

V = volume of *Medium*, 900 mL

L = label claim for each drug substance (mg/Tablet)

M_{r1} = molecular weight of hydrocodone bitartrate disesquihydrate, 494.49

M_{r2} = molecular weight of anhydrous hydrocodone bitartrate, 449.46

Tolerances: NLT 80% (*Q*) of the labeled amounts of hydrocodone bitartrate disesquihydrate ($C_{18}H_{21}NO_3 \cdot C_4H_6O_6 \cdot 2½H_2O$) and homatropine methylbromide ($C_{17}H_{24}BrNO_3$) is dissolved.

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

Medium: Water; 500 mL

Apparatus 2: 50 rpm

Time: 45 min

Mobile phase: 1.4 g/L of octanesulfonic acid sodium salt and 0.1% phosphoric acid in a filtered and degassed mixture of acetonitrile and water (1:3)

Standard solution A: 0.50 mg/mL of USP Hydrocodone Bitartrate RS in *Mobile phase*

Standard solution B: 0.15 mg/mL of USP Homatropine Methylbromide RS in *Mobile phase*

System suitability solution: 0.01 mg/mL of USP Hydrocodone Bitartrate RS and 0.003 mg/mL of USP Homatropine Methylbromide RS prepared as follows. Transfer adequate amounts of *Standard solution A* and *Standard solution B* to a suitable volumetric flask. Add 21% of the total volume of *Mobile phase*, and dilute with *Medium* to volume.

Sample solution: Pass a 20-mL portion of the solution under test through a suitable filter of 0.45-µm pore size, discarding the first 2–3 mL. Mix thoroughly 15.0 mL of the filtrate with 5.0 mL of *Mobile phase*.

Chromatographic system

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

Mode: LC

Detector: UV 212 nm

Column: 3.9-mm × 30-cm; packing L1

Flow rate: 2.0 mL/min

Injection volume: 200 µL

System suitability

Sample: *System suitability solution*

Suitability requirements

Resolution: NLT 2.2 between homatropine methylbromide and hydrocodone bitartrate

Tailing factor: NMT 1.5 for each drug substance

Relative standard deviation: NMT 3.0% for homatropine methylbromide; NMT 2.0% for hydrocodone bitartrate

Analysis

Samples: *Standard solution A*, *Standard solution B*, and *Sample solution*

Calculate the percentage of the labeled amounts of hydrocodone bitartrate disesquihydrate ($C_{18}H_{21}NO_3 \cdot C_4H_6O_6 \cdot 2½H_2O$) and homatropine methylbromide ($C_{17}H_{24}BrNO_3$) dissolved:

$$\text{Result} = (r_U/r_S) \times C_S \times D \times V \times (1/L) \times (M_{r1}/M_{r2}) \times 100$$

r_U = peak area of hydrocodone bitartrate or homatropine methylbromide from the *Sample solution*

r_S = peak area of hydrocodone bitartrate or homatropine methylbromide from the *Standard solution*

C_S = concentration of USP Hydrocodone Bitartrate RS or USP Homatropine Methylbromide RS in the *Standard solution* (mg/mL)

D = dilution factor of the *Sample solution*

V = volume of *Medium*, 500 mL

L = label claim for each drug substance (mg/Tablet)

M_{r1} = molecular weight of hydrocodone bitartrate disesquihydrate, 494.49

M_{r2} = molecular weight of anhydrous hydrocodone bitartrate, 449.46

Tolerances: NLT 75% (*Q*) of the labeled amounts of hydrocodone bitartrate disesquihydrate ($C_{18}H_{21}NO_3 \cdot C_4H_6O_6 \cdot 2½H_2O$) and homatropine methylbromide ($C_{17}H_{24}BrNO_3$) is dissolved.

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

IMPURITIES

• **Limit of Dihydrocodeine Bitartrate, Hydrocodone Diol, and Related Substances**

Buffer: 0.005 M sodium 1-octanesulfonate. Adjust with glacial acetic acid to a pH of 2.5 ± 0.1.

Mobile phase: Methanol and *Buffer* (40:60). Add 0.5 mL/L of triethylamine.

System suitability stock solution: 0.02 mg/mL each of hydrocodone diol and USP Dihydrocodeine Bitartrate RS in *Mobile phase*

System suitability solution: 0.1 µg/mL each of hydrocodone diol and USP Dihydrocodeine Bitartrate RS in *Mobile phase* from the *System suitability stock solution*

Standard solution and **Sample solution:** Proceed as directed in the *Assay*.

Chromatographic system

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

Mode: LC

Detector: UV 280 nm

Column: 4.6-mm × 25-cm; 5-µm packing L7

Flow rate: 1.5 mL/min

Injection volume: 200 µL

Run time: NLT 1.7 times the retention time of hydrocodone bitartrate

System suitability

Sample: *System suitability solution*

Suitability requirements

Resolution: NLT 2.0 between hydrocodone diol and dihydrocodeine bitartrate

Relative standard deviation: NMT 5.0% for both hydrocodone diol and dihydrocodeine bitartrate

Analysis

Sample: *Sample solution*

Calculate the percentages of hydrocodone diol and dihydrocodeine bitartrate in the portion of Tablets taken:

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

r_U = peak response of either hydrocodone diol or dihydrocodeine bitartrate from the *Sample solution*

r_T = peak response of hydrocodone bitartrate from the *Sample solution*

Calculate the percentage of each individual related substance in the portion of Tablets taken:

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

r_U = peak response of any individual related substance from the *Sample solution* with a relative retention time of NLT 0.42 in relation to the retention time of hydrocodone bitartrate

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

Acceptance criteria: See *Table 1*.

Table 1

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Hydrocodone diol[a]	0.67	0.5
Dihydrocodeine bitartrate	0.75	1.0
Hydrocodone bitartrate	1.0	—
Any individual related substance	—	0.5
Total impurities	—	1.5

[a] 4,5-Dihydroxy-3-methoxy-17-methylmorphinan-6-one.

Change to read:

• **Limit of Homatropine Hydrobromide and Related Substances**

Buffer: 0.005 M dibasic potassium phosphate. Adjust with phosphoric acid to a pH of 6.4 ± ▲0.1▲ (ERR 1-Jul-2022).

Mobile phase: Acetonitrile and *Buffer* (30:170). Filter and degas.

Standard solution: 0.6 µg/mL of homatropine hydrobromide in *Mobile phase*

Sample solution: Proceed as directed in the *Assay*.

Chromatographic system

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

Mode: LC

Detector: UV 210 nm

Column: 4.6-mm × 25-cm; 5-µm packing L7

Flow rate: 1.5 mL/min

Injection volume: 10 µL

Run time: NLT 1.6 times the retention time of hydrocodone bitartrate

System suitability

Sample: *Standard solution*

Suitability requirements

Relative standard deviation: NMT 5.0%

Analysis

Sample: *Sample solution*

Calculate the percentage of homatropine hydrobromide in the portion of Tablets taken:

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

r_U = peak response of homatropine hydrobromide from the *Sample solution*

r_T = peak response of homatropine methylbromide from the *Sample solution*

Calculate the percentage of each individual related substance in the portion of Tablets taken:

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

r_U = peak response of any individual related substance from the *Sample solution* with a relative retention time less than 0.44 in relation to the retention time of hydrocodone bitartrate

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

Acceptance criteria: See *Table 2*.

Table 2

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Hydrocodone diol[a]	0.39	—
Dihydrocodeine bitartrate[b]	0.40	—
Homatropine methylbromide	0.44	—
Homatropine hydrobromide	0.53	0.5
Hydrocodone bitartrate	1.0	—
Any individual related substance	—	0.5
Total impurities[b]	—	1.5

[a] 4,5-Dihydroxy-3-methoxy-17-methylmorphinan-6-one.

[b] Impurities are quantified in the test for *Limit of Dihydrocodeine Bitartrate, Hydrocodone Diol, and Related Substances* are not included in Total impurities.

- **Limit of Tropine**

Standard stock solution: 150 µg/mL of tropine in diethyl ether

Standard solution 1: 75 µg/mL of tropine from the *Standard stock solution* in diethyl ether

Standard solution 2: 37.5 µg/mL of tropine from the *Standard solution 1* in diethyl ether

Standard solution 3: 18.75 µg/mL of tropine from the *Standard solution 2* in diethyl ether

Standard solution 4: 9.38 µg/mL of tropine from the *Standard solution 3* in diethyl ether

Sample solution: Finely powder 25 Tablets, and add to a centrifuge tube. Pipet 5.0 mL of diethyl ether into the centrifuge tube, mix on a vortex mixer for 5 min, centrifuge, and use the supernatant.

Chromatographic system

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

Application volume: 500 µL

Developing solvent system: Alcohol and ammonium hydroxide (400:100)

Spray reagent: Dissolve 300 mg of platinic acid in 3 mL of diluted hydrochloric acid. Add 97 mL of water and 100 mL of 6% potassium iodide in water, and mix.

Analysis

Samples: *Standard stock solution*, *Standard solution 1*, *Standard solution 2*, *Standard solution 3*, *Standard solution 4*, and *Sample solution*

Apply the *Standard stock solution*, *Standard solution 1*, *Standard solution 2*, *Standard solution 3*, *Standard solution 4*, and *Sample solution* to a TLC plate and proceed as directed in the chapter. After the plate has dried, position it in a chamber saturated with iodine vapor for about 30 min, then place it in a hood to allow the iodine to sublime from the plate, and spray the plate with *Spray reagent* until spots appear.

Acceptance criteria: Any spot from the *Sample solution* occurring at an R_F value corresponding to tropine is not greater in size or intensity than the corresponding spot from *Standard solution 2* (0.5%); NMT 0.5% of tropine.

ADDITIONAL REQUIREMENTS

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

USP Dihydrocodeine Bitartrate RS
USP Homatropine Methylbromide RS
USP Hydrocodone Bitartrate RS

[1] A suitable grade is available from Analytical Research and Testing, Somerville, NJ; Fax: 908-725-8848.

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

Topic/Question	Contact	Expert Committee
HYDROCODONE BITARTRATE AND HOMATROPINE METHYLBROMIDE TABLETS	Documentary Standards Support	SM22020 Small Molecules 2

Chromatographic Database Information: Chromatographic Database

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