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Orphenadrine Citrate, Aspirin, and Caffeine Tablets

DEFINITION

Orphenadrine Citrate, Aspirin, and Caffeine Tablets contain NLT 90.0% and NMT 110.0% each of orphenadrine citrate ($C_{18}H_{23}NO \cdot C_6H_8O_7$), aspirin ($C_9H_8O_4$), and caffeine ($C_8H_{10}N_4O_2$).

IDENTIFICATION

• **A.** The retention times of the orphenadrine, aspirin, and caffeine peaks in the chromatogram of the *Sample solution* correspond to those of the orphenadrine, aspirin, and caffeine peaks in the chromatogram of the *Standard solution*, as obtained in the *Orphenadrine Citrate* and *Aspirin and Caffeine* tests in the *Assay*.

ASSAY

• **Orphenadrine Citrate**

Buffer: 6.8 g/L of monobasic potassium phosphate in water. Adjust with phosphoric acid to a pH of 3.6. To each L of this solution add 5.8 g of sodium dodecyl sulfate, and dissolve.

Mobile phase: Acetonitrile and *Buffer* (50:50)

Diluent: Methanol and glacial acetic acid (92:8)

Standard solution: 0.1 mg/mL of USP Orphenadrine Citrate RS prepared as follows. Transfer the weighed amount of standard to a suitable volumetric flask with the aid of methanol. Add glacial acetic acid to fill 8% of final volume and methanol to fill 75% of final volume. Sonicate with occasional shaking for NLT 15 min. Allow the solution to equilibrate to room temperature. Dilute with methanol to volume. Filter a portion through a suitable filter of 0.45-µm pore size, discarding at least the first 3 mL of the filtrate.

Sample stock solution: Nominally 0.5 mg/mL of orphenadrine citrate from Tablets (NLT 5), prepared as follows. To the volumetric flask containing the Tablets, add glacial acetic acid to fill 8% of final volume and methanol to fill 75% of final volume. Sonicate with occasional hand shaking for NLT 15 min. Shake mechanically for NLT 15 min. Allow the solution to equilibrate to room temperature. Dilute with methanol to volume. [Note—This solution also contains 7.7 mg/mL of aspirin and 0.6 mg/mL of caffeine.]

Sample solution: Nominally 0.1 mg/mL of orphenadrine citrate by diluting a suitable portion of the *Sample stock solution* with *Diluent.* Filter a portion through a suitable filter of 0.45-µm pore size, discarding at least the first 3 mL of the filtrate. [Note—This solution also contains 1.5 mg/mL of aspirin and 0.1 mg/mL of caffeine.]

Chromatographic system

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

Mode: LC

Detector: UV 257 nm

Column: 3.9-mm × 30-cm; 10-µm packing L1

Flow rate: 2 mL/min

Injection volume: 15 µL

Run time: 1.5 times the retention time of orphenadrine

System suitability

Sample: *Standard solution*

Suitability requirements

Tailing factor: NMT 1.5

Relative standard deviation: NMT 2.0%

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of orphenadrine citrate ($C_{18}H_{23}NO \cdot C_6H_8O_7$) in the portion of Tablets taken:

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

r_U = peak response from the *Sample solution*

r_S = peak response from the *Standard solution*

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

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

Acceptance criteria: 90.0%–110.0%

- **Aspirin and Caffeine**

Buffer: Dissolve 0.8 g/L of hexanesulfonic acid sodium salt in water. Adjust with glacial acetic acid to a pH of 3.0.

Mobile phase: Methanol and *Buffer* (40:60)

Diluent: Methanol and glacial acetic acid (92:8)

Standard solution: 1.5 mg/mL of USP Aspirin RS and 0.1 mg/mL of USP Caffeine RS prepared as follows. Transfer the weighed amount of standards to a suitable volumetric flask with the aid of methanol. Add glacial acetic acid to fill 8% of final volume and methanol to fill 75% of final volume. Sonicate with occasional hand shaking for NLT 15 min. Allow the solution to equilibrate to room temperature. Dilute with methanol to volume. Filter a portion through a suitable filter of 0.45-µm pore size, discarding at least the first 3 mL of the filtrate.

Sample stock solution: Nominally 7.7 mg/mL of aspirin from Tablets (NLT 5), prepared as follows. To the volumetric flask containing the Tablets, add glacial acetic acid to fill 8% of final volume and methanol to fill 75% of final volume. Sonicate with occasional hand shaking for NLT 15 min. Allow the solution to equilibrate to room temperature. Dilute with methanol to volume. [Note—This solution also contains 0.6 mg/mL of caffeine and 0.5 mg/mL of orphenadrine citrate.]

Sample solution: Nominally 1.5 mg/mL of aspirin by diluting a suitable portion of the *Sample stock solution* with *Diluent.* Filter a portion through a suitable filter of 0.45-µm pore size, discarding at least the first 3 mL of the filtrate. [Note—This *Sample solution* also contains 0.1 mg/mL of caffeine and 0.1 mg/mL of orphenadrine citrate.]

Chromatographic system

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

Mode: LC

Detector: UV 254 nm

Column: 3.9-mm × 30-cm; 10-µm packing L1

Flow rate: 1.2 mL/min

Injection volume: 15 µL

Run time: 3 times the retention time of aspirin

System suitability

[Note—The relative retention time for caffeine and for aspirin is 0.70 and 1.0, respectively.]

Sample: *Standard solution*

Suitability requirements

Resolution: NLT 1.5 between caffeine and aspirin peaks

Relative standard deviation: NMT 2.0% each for both the caffeine and aspirin peaks

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of aspirin ($C_9H_8O_4$) in the portion of Tablets taken:

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

r_U = peak response from the *Sample solution*

r_S = peak response from the *Standard solution*

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

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

Calculate the percentage of the labeled amount of caffeine ($C_8H_{10}N_4O_2$) in the portion of Tablets taken:

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

r_U = peak response from the *Sample solution*

r_S = peak response from the *Standard solution*

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

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

Acceptance criteria: 90.0%–110.0% each of aspirin and caffeine

PERFORMANCE TESTS

• **Dissolution ⟨711⟩**

Medium: Water; 900 mL

Apparatus 2: 50 rpm

Times: 45 min for aspirin and caffeine; 60 min for orphenadrine

Separate dissolution baths must be run for the different time points.

Orphenadrine citrate

Buffer: 6.8 g/L of monobasic potassium phosphate in water. Adjust with phosphoric acid to a pH of 3.6. To each L of this solution add 5.8 g of sodium dodecyl sulfate, and dissolve.

Mobile phase: Acetonitrile and *Buffer* (50:50)

Standard solution: (*L*/900) mg/mL of USP Orphenadrine Citrate RS in *Medium*, where *L* is the label claim in mg/Tablet

Sample solution: Pass a portion of the solution under test through a suitable filter.

Chromatographic system

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

Mode: LC

Detector: UV 257 nm

Column: 3.9-mm × 30-cm; 10-µm packing L1

Flow rate: 2 mL/min

Injection volume: 100 µL

Run time: 1.2 times the retention time of orphenadrine

System suitability

Sample: *Standard solution*

Suitability requirements

Tailing factor: NMT 1.5

Relative standard deviation: NMT 3.0%

Calculate the percentage (*Q*) of the labeled amount of orphenadrine citrate ($C_{18}H_{23}NO \cdot C_6H_8O_7$) dissolved:

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

r_U = peak response for orphenadrine from the *Sample solution*

r_S = peak response for orphenadrine from the *Standard solution*

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

L = label claim for orphenadrine (mg/Tablet)

V = volume of *Medium*, 900 mL

Tolerances: NLT 75% (*Q*) of the labeled amount of orphenadrine is dissolved in 60 min.

Aspirin and caffeine

Buffer: 0.8 g/L of hexanesulfonic acid sodium salt in water

Mobile phase: Methanol and *Buffer* (40:60). Adjust with glacial acetic acid to a pH of 3.0.

Standard stock solution: 1.0 mg/mL of USP Aspirin RS, 0.1 mg/mL of USP Caffeine RS, and 0.1 mg/mL of USP Salicylic Acid RS prepared as follows. Transfer the weighed amount of standards to a suitable volumetric flask with the aid of methanol. Add glacial acetic acid to fill 8% of final volume and methanol to fill 75% of final volume. Sonicate with occasional shaking for NLT 15 min. Allow the solution to equilibrate to room temperature. Dilute with methanol to volume.

Standard solution: Dilute a suitable volume of the *Standard stock solution* with methanol to obtain a final concentration of about 0.25 mg/mL of USP Aspirin RS and 0.025 mg/mL each of USP Caffeine RS and USP Salicylic Acid RS.

Sample solution: At the time specified, withdraw the solution under test and pass through a suitable filter. If necessary, dilute the filtrate with methanol to obtain a final concentration similar to that of the *Standard solution*.

Chromatographic system

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

Mode: LC

Detector: UV 254 nm

Column: 3.9-mm × 30-cm; 10-µm packing L1

Flow rate: 1.2 mL/min

Injection volume: 15 µL

Run time: 2 times the retention time of aspirin

System suitability

[Note—The relative retention times for caffeine, aspirin, and salicylic acid are 0.70, 1.0, and 1.3, respectively.]

Sample: *Standard solution*

Suitability requirements

Relative standard deviation: NMT 3.0% for both the caffeine and aspirin peaks

Calculate the percentage (Q) of the labeled amount of aspirin ($C_9H_8O_4$) or caffeine ($C_8H_{10}N_4O_2$) dissolved:

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

r_U = peak response for aspirin or caffeine from the *Sample solution*

r_S = peak response for aspirin or caffeine from the *Standard solution*

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

L = label claim for aspirin or caffeine (mg/Tablet)

D = dilution factor, if applicable

V = volume of *Medium*, 900 mL

Calculate the percentage of salicylic acid ($C_7H_6O_3$), relative to the labeled amount of aspirin, dissolved:

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

r_U = peak response for salicylic acid from the *Sample solution*

r_S = peak response for salicylic acid from the *Standard solution*

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

L = label claim for aspirin (mg/Tablet)

D = dilution factor

M_{r1} = molecular weight of aspirin, 180.16

M_{r2} = molecular weight of salicylic acid, 138.12

V = volume of *Medium*, 900 mL

The percentage of salicylic acid dissolved should be added to the percentage of aspirin dissolved.

Tolerances: NLT 70% (Q) of the labeled amounts of aspirin and caffeine is dissolved in 45 min.

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

IMPURITIES

Change to read:

• **Limit of 2-Methylbenzhydrol**

Buffer: 6.8 g/L of monobasic potassium phosphate in water

Mobile phase: To 1 L of *Buffer* add 5.8 g of sodium dodecyl sulfate and 1 L of acetonitrile. Adjust with phosphoric acid to a pH of 3.6.

Standard solution: 7.5 µg/mL of ▲USP Methylbenzhydrol RS▲ (ERR 1-Apr-2023) in methanol

Sample solution: Nominally 1.5 mg/mL of orphenadrine citrate in methanol from a portion of finely powdered Tablets (NLT 20 Tablets). [Note—This *Sample solution* also contains 0.6 mg/mL of caffeine and 0.5 mg/mL of orphenadrine citrate.]

Chromatographic system

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

Mode: LC

Detector: UV 213 nm

Column: 4.6-mm × 150-mm; 5-µm packing L1

Flow rate: 1.2 mL/min

Injection volume: 10 µL

Run time: 2.5 times the retention time of 2-methyl benzhydrol

System suitability

Sample: *Standard solution*

Suitability requirements:

Tailing factor: NMT 1.5

Relative standard deviation: NMT 5.0%

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of 2-methylbenzhydrol in the portion of Tablets taken:

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

r_U = peak response from the *Sample solution*

r_S = peak response from the *Standard solution*

C_S = concentration of ▲USP Methylbenzhydrol RS▲ (ERR 1-Apr-2023) in the *Standard solution* (mg/mL)

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

Acceptance criteria: NMT 0.5%

- **Organic Impurities**

Buffer: 0.8 g/L of sodium 1-hexanesulfonate in water. Adjust with glacial acetic acid to a pH of 3.0.

Mobile phase: Methanol and *Buffer* (40:60)

Diluent: Methanol and glacial acetic acid (92:8)

System suitability solution: 0.6 mg/mL of USP Salicylic Acid RS, 1.5 mg/mL of USP Aspirin RS, and 0.1 mg/mL of USP Caffeine RS prepared as follows. Transfer the weighed amount of standards to a suitable volumetric flask with the aid of methanol. Add glacial acetic acid to fill 8% of final volume and methanol to fill 75% of final volume. Sonicate with occasional hand shaking for NLT 15 min. Allow the solution to equilibrate to room temperature. Dilute with methanol to volume. Filter a portion through a suitable filter of 0.45-µm pore size, discarding at least the first 3 mL of the filtrate.

Standard solution: 0.04 mg/mL of USP Salicylic Acid RS prepared as follows. Transfer the weighed amount of standard to a suitable volumetric flask with the aid of methanol. Add glacial acetic acid to fill 8% of final volume, and dilute with methanol to volume. Filter a portion through a suitable filter of 0.45-µm pore size, discarding at least the first 3 mL of the filtrate.

Sample stock solution: Nominally 7.7 mg/mL of aspirin from Tablets (NLT 5), prepared as follows. To the volumetric flask containing the Tablets, add glacial acetic acid to fill 8% of final volume and methanol to fill 75% of final volume. Sonicate with occasional hand shaking for NLT 15 min. Allow the solution to equilibrate to room temperature. Dilute with methanol to volume. [Note—This solution also contains 0.5 mg/mL of orphenadrine citrate and 0.6 mg/mL of caffeine.]

Sample solution: Nominally 1.5 mg/mL of aspirin by diluting a suitable portion of the *Sample stock solution* with *Diluent*. Filter a portion through a suitable filter of 0.45-µm pore size, discarding at least the first 3 mL of the filtrate. [Note—This *Sample solution* also contains 0.1 mg/mL of orphenadrine citrate and 0.1 mg/mL of caffeine.]

Chromatographic system

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

Mode: LC

Detector: UV 254 nm

Column: 3.9-mm × 30-cm; 10-µm packing L1

Flow rate: 1.2 mL/min

Injection volume: 25 µL

Run time: 3 times the retention time of the aspirin peak

System suitability

[Note—Refer to *Table 1* for relative retention times.]

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

Suitability requirements

Resolution: NLT 1.5 between the caffeine and aspirin peaks and NLT 1.5 between the aspirin and salicylic acid peaks, *System suitability solution*

Relative standard deviation: NMT 2.0% each for aspirin and caffeine peaks, *System suitability solution;* NMT 3.0% for salicylic acid, *Standard solution*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of salicylic acid in the portion of Tablets taken:

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

r_U = peak response from the *Sample solution*

r_S = peak response from the *Standard solution*

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

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

Calculate the percentage of other organic impurities in the portion of Tablets taken:

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

r_U = sum of the areas of all other organic impurities from the *Sample solution*

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

Acceptance criteria: See *Table 1*.

Table 1

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Caffeine	0.70	—
Aspirin	1.0	—
Salicylic acid	1.3	3.0
Total impurities[a]	—	2.0

[a] Does not include salicylic acid and 2-methylbenzhydrol.

ADDITIONAL REQUIREMENTS

• **Packaging and Storage:** Preserve in tight containers. Store at controlled room temperature.

Change to read:

• **USP Reference Standards** ⟨11⟩

USP Aspirin RS

USP Caffeine RS

▲USP Methylbenzhydrol RS▲ (ERR 1-Apr-2023)

2-Methylbenzhydrol.

$C_{14}H_{14}O$ 198.26

USP Orphenadrine Citrate RS

USP Salicylic Acid RS

Topic/Question	Contact	Expert Committee
ORPHENADRINE CITRATE, ASPIRIN, AND CAFFEINE TABLETS	Documentary Standards Support	SM42020 Small Molecules 4
REFERENCE STANDARD SUPPORT	RS Technical Services RSTECH@usp.org	SM42020 Small Molecules 4

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