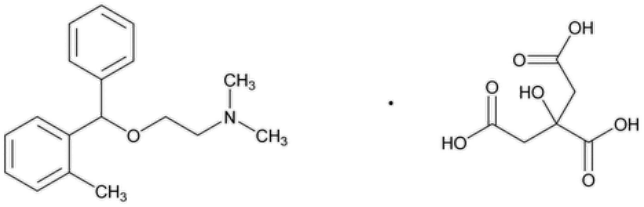
Status: Currently Official on 16-Feb-2025
Official Date: Official as of 01-May-2020
Document Type: USP Monographs
DocId: GUID-0DD3EF2C-AB4D-4B27-B2C6-7C1455B5BA96_2_en-US
DOI: https://doi.org/10.31003/USPNF_M58870_02_01
DOI Ref: 4hf8y



# Orphenadrine Citrate



$C_{18}H_{23}NO \cdot C_6H_8O_7$ 461.50

Ethanamine, *N*,*N*-dimethyl-2-[(2-methylphenyl)phenylmethoxy]-, (±)-, 2-hydroxy-1,2,3-propanetricarboxylate (1:1);

(±)-*N*,*N*-Dimethyl-2-[(*o*-methyl-α-phenylbenzyl)oxy]ethylamine citrate (1:1) CAS RN®: 4682-36-4; UNII: X0A40N8I4S.

## DEFINITION

Orphenadrine Citrate contains NLT 98.0% and NMT 101.5% of orphenadrine citrate ($C_{18}H_{23}NO \cdot C_6H_8O_7$), calculated on the dried basis.

## IDENTIFICATION

***Change to read:***

• **A.** ▲**Spectroscopic Identification Tests ⟨197⟩, *Infrared Spectroscopy*: 197M**▲ (CN 1-May-2020)

• **B.** The retention time of the major peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay*.

• **C.** **Identification Tests—General, *Citrate*⟨191⟩:** Meets the requirements

## ASSAY

• **Procedure**

**Buffer:** 5.8 g/L of monobasic ammonium phosphate in water. Adjust with ammonium hydroxide or phosphoric acid to a pH of 7.9.

**Mobile phase:** Methanol, acetonitrile, and *Buffer* (45:15:40)

**System suitability solution:** 0.01 mg/mL each of USP Orphenadrine Related Compound B RS, USP Orphenadrine Related Compound C RS, and USP Methylbenzhydrol RS and 1.0 mg/mL of USP Orphenadrine Citrate RS in *Mobile phase*

**Standard solution:** 1.0 mg/mL of USP Orphenadrine Citrate RS in *Mobile phase*

**Sample solution:** 1.0 mg/mL of Orphenadrine Citrate in *Mobile phase*

**Chromatographic system**

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

**Mode:** LC

**Detector:** UV 220 nm

**Column:** 4.6-mm × 15-cm; 5-µm packing L1

**Column temperature:** 40°

**Flow rate:** 1.5 mL/min

**Injection volume:** 20 µL

**Run time:** NLT 2.5 times the retention time of orphenadrine

**System suitability**

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

[Note—See *Table 1* for the relative retention times.]

**Suitability requirements**

**Resolution:** NLT 3.0 between orphenadrine related compound B and C; NLT 3.0 between orphenadrine related compound C and methylbenzhydrol, *System suitability solution*

**Tailing factor:** NMT 2.0, *Standard solution*

**Relative standard deviation:** NMT 0.73%, *Standard solution*

**Analysis**

**Samples:** *Standard solution* and *Sample solution*

Calculate the percentage of orphenadrine citrate ($C_{18}H_{23}NO \cdot C_6H_8O_7$) in the portion of Orphenadrine Citrate 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)

$C_U$ = concentration of Orphenadrine Citrate in the *Sample solution* (mg/mL)

**Acceptance criteria:** 98.0%–101.5% on the dried basis

## IMPURITIES

• **Residue on Ignition ⟨281⟩:** NMT 0.1%

• **Organic Impurities, Procedure 1**

[Note—If methyl orphenadrine is a known manufacturing impurity, *Procedure 1* and the test for *Isomer Content* are recommended. If diphenhydramine and didesmethyl orphenadrine are known manufacturing process impurities, *Procedure 2* is recommended.]

**Buffer, Mobile phase, System suitability solution,** and **Chromatographic system:** Proceed as directed in the *Assay*.

**Standard solution:** 0.001 mg/mL of USP Orphenadrine Citrate RS in *Mobile phase*

**Sensitivity solution:** 0.5 µg/mL of USP Orphenadrine Citrate RS, from the *Standard solution*, in *Mobile phase*

**Sample solution:** 1 mg/mL of Orphenadrine Citrate in *Mobile phase*

**System suitability**

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

[Note—See *Table 1* for the relative retention times.]

**Suitability requirements**

**Resolution:** NLT 3.0 between orphenadrine related compound B and C; NLT 3.0 between orphenadrine related compound C and 2-methylbenzhydrol, *System suitability solution*

**Tailing factor:** NMT 2, *Standard solution*

**Relative standard deviation:** NMT 5.0%, *Standard solution*

**Signal-to-noise ratio:** NLT 10, *Sensitivity solution*

**Analysis**

**Samples:** *Standard solution* and *Sample solution*

Calculate the percentage of each impurity in the portion of Orphenadrine Citrate taken:

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

$r_U$ = peak area of each impurity from the *Sample solution*

$r_S$ = peak area of Orphenadrine Citrate from the *Standard solution*

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

$C_U$ = concentration of the *Sample solution* (mg/mL)

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

**Acceptance criteria:** See *Table 1*. Disregard any peak less than 0.05%.

**Table 1**

| Name | Relative Retention Time | Relative Response Factor | Acceptance Criteria, NMT (%) |
|---|---|---|---|
| Citric acid[a] | 0.14 | — | — |

| Name | Relative Retention Time | Relative Response Factor | Acceptance Criteria, NMT (%) |
|---|---|---|---|
| Orphenadrine related compound B | 0.25 | 1.3 | 0.1 |
| Orphenadrine related compound C | 0.39 | 1.0 | 0.3 |
| Methylbenzhydrol | 0.51 | 2.4 | 0.1 |
| Diphenhydramine | 0.69 | 1.0 | 0.3 |
| Orphenadrine | 1.0 | — | — |
| Methyl orphenadrine[b] | 1.54 | 1.9 | 0.1 |
| Any individual unspecified impurity | — | 1.0 | 0.10 |
| Total impurities[c] | — | — | 0.5 |

[a] Counter ion peak; not to be reported; not to be included in total impurities.

[b] 2-(Di-*o*-tolylmethoxy)-*N*,*N*-dimethylethan-1-amine.

[c] Excluding orphenadrine related compound E and orphenadrine related compound F from the *Isomer Content* test.

• **Organic Impurities, Procedure 2**

[Note—If didesmethyl orphenadrine is a known manufacturing process impurity, *Procedure 2* is recommended. The labeling indicates that the article complies with *Organic Impurities, Procedure 2*.]

**System suitability solution:** 0.3 mg/mL each of USP Orphenadrine Citrate RS, USP Diphenhydramine Citrate RS, USP Methylbenzhydrol RS, USP Orphenadrine Related Compound E RS, and USP Orphenadrine Related Compound F RS in toluene prepared as follows. Dissolve 6 mg each of the USP Reference Standards in 10 mL of water. Add 0.2 mL of ammonium hydroxide and shake with 3 mL of toluene. Separate the organic layer. Repeat the extraction of the aqueous layer two more times with 3 mL of toluene. To the combined organic layer add anhydrous sodium sulfate, shake, and filter. Evaporate the filtrate at NMT 50° using a rotary evaporator. Dissolve the residue in 20 mL of toluene.

**Sample solution:** 25 mg/mL of Orphenadrine Citrate in toluene prepared as follows. Dissolve 500 mg of Orphenadrine Citrate in 50 mL of water. Add 2 mL of ammonium hydroxide and shake with 10 mL of toluene. Separate the organic layer. Repeat the extraction of the aqueous layer two more times with 10 mL of toluene. To the combined organic layers add anhydrous sodium sulfate, shake, and filter. Evaporate the filtrate at NMT 50° using a rotary evaporator. Dissolve the residue in 20 mL of toluene.

**Chromatographic system**

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

**Mode:** GC

**Detector:** Flame ionization

**Column:** 0.32-mm × 60-m; 1-µm thick coating of phenyl methylpolysiloxane, phase G27

**Carrier gas:** Helium at 1 mL/min

**Temperatures**

**Injection port:** 290°

**Detector:** 290°

**Column:** 240°

**Injection volume:** 2 µL

**Injection type:** Split ratio, 1:25

**Run time:** 1.3 times the retention time of orphenadrine

**System suitability**

**Sample:** *System suitability solution*

[Note—Relative retention times for the peaks are given in *Table 2*.]

**Suitability requirements**

**Resolution:** NLT 1.5 between orphenadrine related compound E and orphenadrine; NLT 2.0 between orphenadrine and orphenadrine related compound F

**Analysis**

**Sample:** *Sample solution*

Calculate the sum of the percentage of any individual impurity in the portion of Orphenadrine Citrate taken:

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

$r_U$ = peak response of the impurity from the *Sample solution*

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

**Acceptance criteria:** See *Table 2*. Disregard any peak less than 0.05%.

**Table 2**

| Name | Relative Retention Time | Acceptance Criteria, NMT (%, w/w) |
|---|---|---|
| Methylbenzophenone[a] | 0.5 | 0.3 |
| Methylbenzhydrol | 0.6 | 0.3 |
| Diphenhydramine | 0.8 | 0.3 |
| Didesmethyl orphenadrine[b] | 0.9 | 0.3 |
| Orphenadrine related compound E | 0.98 | 0.3 |
| Orphenadrine | 1.0 | — |
| Orphenadrine related compound F | 1.1 | 0.3 |
| Any individual unspecified impurity | — | 0.10 |
| Total impurities | — | 1.0 |

[a] Phenyl(*o*-tolyl)methanone.

[b] 2-[Phenyl(*o*-tolyl)methoxy]ethanamine.

• **Isomer Content**

If methyl orphenadrine is a known manufacturing impurity, the test for *Isomer Content* is to be performed.

**System suitability solution:** 0.3 mg/mL each of USP Orphenadrine Citrate RS, USP Orphenadrine Related Compound E RS, and USP Orphenadrine Related Compound F RS in toluene prepared as follows. Dissolve 6 mg each of the USP Reference Standards in 10 mL of water. Add 0.2 mL of ammonium hydroxide and shake with 3 mL of toluene. Separate the organic layer. Repeat the extraction of the aqueous layer two more times with 3 mL of toluene. To the combined organic layer add anhydrous sodium sulfate, shake, and filter. Evaporate the filtrate at NMT 50° using a rotary evaporator. Dissolve the residue in 20 mL of toluene.

**Sample solution** and **Chromatographic system:** Proceed as directed in *Organic Impurities, Procedure 2*.

**System suitability**

**Sample:** *System suitability solution*

[Note—The relative retention times of orphenadrine related compound E, orphenadrine, and orphenadrine related compound F are about 0.98, 1.0, and 1.1, respectively.]

**Suitability requirements**

**Resolution:** NLT 1.5 between orphenadrine related compound E and orphenadrine; NLT 2.0 between orphenadrine and orphenadrine related compound F

**Analysis**

**Sample:** *Sample solution*

Calculate the percentage of orphenadrine related compound E and orphenadrine related compound F in the portion of Orphenadrine Citrate taken:

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

$r_U$ = peak response of orphenadrine related compound E or orphenadrine related compound F from the *Sample solution*

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

**Acceptance criteria:** NMT 0.3% each of orphenadrine related compound E and orphenadrine related compound F

## SPECIFIC TESTS

• **Loss on Drying ⟨731⟩**

**Analysis:** Dry at 105° for 3 h.

**Acceptance criteria:** NMT 0.5%

## ADDITIONAL REQUIREMENTS

• **Packaging and Storage:** Preserve in tight, light-resistant containers.

• **Labeling:** The label states with which *Organic Impurities* procedure the article complies if *Organic Impurities, Procedure 1*, is not used.

• **USP Reference Standards ⟨11⟩**

USP Diphenhydramine Citrate RS

USP Methylbenzhydrol RS

2-Methylbenzhydrol;
Also known as Phenyl(*o*-tolyl)methanol.
$C_{14}H_{14}O$ 198.26

USP Orphenadrine Citrate RS

USP Orphenadrine Related Compound B RS

*N*-Ethyl-*N*,*N*-dimethyl-2-[phenyl(*o*-tolyl)methoxy]ethanaminium chloride.
$C_{20}H_{28}ClNO$ 333.90

USP Orphenadrine Related Compound C RS

*N*-Methyl-2-[phenyl(*o*-tolyl)methoxy]ethanamine hydrochloride.
$C_{17}H_{21}NO \cdot HCl$ 291.82

USP Orphenadrine Related Compound E RS

*N*,*N*-Dimethyl-2-[phenyl(*m*-tolyl)methoxy]ethanamine.
$C_{18}H_{23}NO$ 269.38

USP Orphenadrine Related Compound F RS

*N*,*N*-Dimethyl-2-[phenyl(*p*-tolyl)methoxy]ethanamine.
$C_{18}H_{23}NO$ 269.38



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

| Topic/Question | Contact | Expert Committee |
|---|---|---|
| ORPHENADRINE CITRATE | Documentary Standards Support | SM42020 Small Molecules 4 |
| REFERENCE STANDARD SUPPORT | RS Technical Services<br>RSTECH@usp.org | SM42020 Small Molecules 4 |

**Chromatographic Database Information:** Chromatographic Database

**Most Recently Appeared In:**
Pharmacopeial Forum: Volume No. PF 41(1)

**Current DocID: GUID-0DD3EF2C-AB4D-4B27-B2C6-7C1455B5BA96_2_en-US**

**DOI: https://doi.org/10.31003/USPNF_M58870_02_01**

**DOI ref: 4hf8y**