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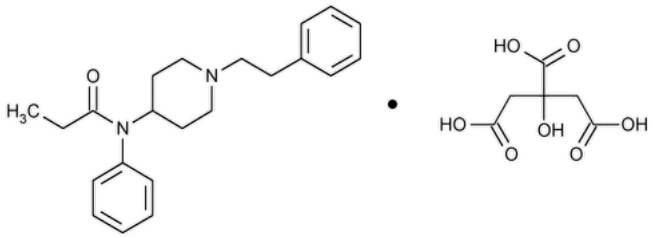
Fentanyl Citrate

Change to read:



$C_{22}H_{28}N_2O \cdot C_6H_8O_7$ ▲528.60▲ (ERR 1-May-2021)

Propanamide, *N*-phenyl-*N*-[1-(2-phenylethyl)-4-piperidinyl]-, 2-hydroxy-1,2,3-propanetricarboxylate (1:1);
N-(1-Phenethyl-4-piperidyl)propionanilide citrate (1:1);
▲*N*-(1-Phenethylpiperidin-4-yl)-*N*-phenylpropionamide 2-hydroxy-1,2,3-propanetricarboxylate▲ (USP 1-May-2021) CAS RN®: 990-73-8; UNII: MUN5LYG46H.

DEFINITION

Fentanyl Citrate contains NLT 98.0% and NMT 102.0% of fentanyl citrate ($C_{22}H_{28}N_2O \cdot C_6H_8O_7$), calculated on the dried basis.

[**Caution—**Great care should be taken to prevent inhaling particles of Fentanyl Citrate and exposing the skin to it.]

IDENTIFICATION

Change to read:

• **A. Spectroscopic Identification Tests ⟨197⟩, *Infrared Spectroscopy*:** 197K ▲or 197A▲ (USP 1-May-2021)

Delete the following:

▲• **B. Spectroscopic Identification Tests ⟨197⟩, Ultraviolet-Visible Spectroscopy:** 197U

Medium: Dilute hydrochloric acid in methanol (1 in 10)

Standard solution: 500 µg/mL of USP Fentanyl Citrate RS in *Medium*

Sample solution: 500 µg/mL of Fentanyl Citrate in *Medium*

Acceptance criteria: Meets the requirements▲ (USP 1-May-2021)

Add the following:

▲• **B.** The retention time of the major peak of the *Sample solution* corresponds to that of the *Standard solution* as obtained in the Assay.▲ (USP 1-May-2021)

ASSAY

Change to read:

• **Procedure**

▲[Note—The use of high purity (such as HPLC-grade) ammonium formate and ultratrace ammonium hydroxide is recommended.]

Buffer: Dissolve 2.52 g of ammonium formate with 4 L of water.

Solution A: Acetonitrile and *Buffer* (5:95). Adjust with ammonium hydroxide to a pH of 9.5.

Solution B: Acetonitrile and *Buffer* (95:5). Adjust with ammonium hydroxide to a pH of 9.5.

Mobile phase: See *Table 1*.

Table 1

Time (min)	Solution A (%)	Solution B (%)
0	85	15
9	65	35

Time (min)	Solution A (%)	Solution B (%)
33	50	50
38	50	50
38.1	85	15
45	85	15

Diluent: Acetonitrile, water, and trifluoroacetic acid (5: 95: 0.025)

Standard solution: 1.6 mg/mL of USP Fentanyl Citrate RS prepared as follows. Transfer a suitable quantity of USP Fentanyl Citrate RS to an adequate volumetric flask. Dissolve with 90% of the flask volume of *Diluent*, and dilute with acetonitrile to volume. Sonicate if necessary.

Sample solution: 1.6 mg/mL of Fentanyl Citrate prepared as follows. Transfer a suitable quantity of Fentanyl Citrate to an adequate volumetric flask. Dissolve with 90% of the flask volume of *Diluent*, and dilute with acetonitrile to volume. Sonicate if necessary.

Chromatographic system

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

Mode: LC

Detector: UV 260 nm

Column: 4.6-mm × 15-cm; 3.5-µm packing L1

Column temperature: 45°

Flow rate: 1.0 mL/min

Injection volume: 40 µL

System suitability

Sample: *Standard solution*

Suitability requirements

Tailing factor: NMT 2.5

Relative standard deviation: NMT 0.73%

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of fentanyl citrate ($C_{22}H_{28}N_2O \cdot C_6H_8O_7$) in the portion of Fentanyl Citrate taken:

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

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

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

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

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

▲ (USP 1-May-2021)

Acceptance criteria: 98.0%–102.0% on the dried basis

IMPURITIES

• **Residue on Ignition ⟨281⟩:** NMT 0.5%

Delete the following:

▲• **Ordinary Impurities ⟨466⟩**

Standard solution: In a mixture of chloroform and methanol (80:20). Eliminate the 0.01 mg/mL solution, and add a 0.02 mg/mL solution.

Sample solution: In a mixture of chloroform and methanol (80:20)

Analysis: Use a thin-layer chromatographic plate coated with chromatographic silica gel with a calcium sulfate binder.

Eluant: Chloroform, methanol, and formic acid (85:10:5)

Visualization: 3

Acceptance criteria: Meets the requirements▲ (USP 1-May-2021)

Change to read:

• ▲**Organic Impurities**

Buffer, Solution A, Solution B, Mobile phase, Diluent, and **Sample solution:** Prepare as directed in the *Assay*.

Standard stock solution 1: 50 µg/mL of USP Fentanyl Related Compound E RS prepared as follows. Transfer a suitable quantity of USP Fentanyl Related Compound E RS to an adequate volumetric flask. Dissolve with 10% of the flask volume of acetonitrile. Sonicate if necessary. Dilute with *Diluent* to volume.

Standard stock solution 2: 50 µg/mL of USP Fentanyl Related Compound G RS prepared as follows. Transfer a suitable quantity of USP Fentanyl Related Compound G RS to an adequate volumetric flask. Dissolve with 10% of the flask volume of acetonitrile. Sonicate if necessary. Dilute with *Diluent* to volume.

Sensitivity solution: 0.5 µg/mL of USP Fentanyl Related Compound G RS prepared as follows. Dilute *Standard stock solution 2* with *Diluent*.

Standard solution: 2.0 µg/mL each of USP Fentanyl Related Compound E RS and USP Fentanyl Related Compound G RS prepared as follows. Transfer suitable volumes of *Standard stock solution 1* and *Standard stock solution 2* to an adequate volumetric flask. Dilute with *Diluent* to volume.

Chromatographic system: Proceed as directed in the *Assay*, except for the *Detector*.

Detector: UV 240 nm

System suitability

Samples: *Sensitivity solution* and *Standard solution*

Suitability requirements

Relative standard deviation: NMT 5.0% for fentanyl related compound E and fentanyl related compound G, *Standard solution*

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

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of fentanyl related compound E relative to fentanyl in the portion of Fentanyl Citrate taken:

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

r_U = peak response of fentanyl related compound E from the *Sample solution*

r_S = peak response of fentanyl related compound E from the *Standard solution*

C_S = concentration of USP Fentanyl Related Compound E RS in the *Standard solution* (mg/mL)

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

M_{r1} = molecular weight of fentanyl citrate, ▲528.60▲ (ERR 1-May-2021)

M_{r2} = molecular weight of fentanyl, ▲336.48▲ (ERR 1-May-2021)

Calculate the percentage of any other specified or unspecified impurity relative to fentanyl in the portion of Fentanyl Citrate taken:

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

r_U = peak response of any other specified or unspecified impurity from the *Sample solution*

r_S = peak response of fentanyl related compound G from the *Standard solution*

C_S = concentration of USP Fentanyl Related Compound G RS in the *Standard solution* (mg/mL)

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

M_{r1} = molecular weight of fentanyl citrate, ▲528.60▲ (ERR 1-May-2021)

M_{r2} = molecular weight of fentanyl, ▲336.48▲ (ERR 1-May-2021)

F = relative response factor (see *Table 2*)

Acceptance criteria: See *Table 2*. The reporting threshold is 0.05%.

Table 2

Name	Relative Retention Time	Relative Response Factor[a]	Acceptance Criteria, NMT (%)[b]
Citric acid[c]	0.04	—	—
Fentanyl *N*-oxide[d]	0.26	0.69	0.15
Fentanyl related compound G	0.78	1.0	0.15
Fentanyl pyruvyl analog[e]	0.92	3.0	0.15

Name	Relative Retention Time	Relative Response Factor[a]	Acceptance Criteria, NMT (%)[b]
Fentanyl	1.00	—	—
Fentanyl related compound E	1.14	—	0.15
Fentanyl butyryl analog[f]	1.21	1.5	0.15
Any unspecified impurity	—	1.0	0.10
Total impurities	—	—	0.50

[a] The relative response factor is calculated relative to fentanyl related compound G.

[b] The (% w/w) is calculated relative to fentanyl.

[c] This peak is due to the counter ion of citrate. It is for peak identification only.

[d] 1-Phenethyl-4-(*N*-phenylpropionamido)piperidine 1-oxide.

[e] 2-Oxo-*N*-(1-phenethylpiperidin-4-yl)-*N*-phenylpropanamide.

[f] *N*-(1-Phenethylpiperidin-4-yl)-*N*-phenylbutyramide.

▲ (USP 1-May-2021)

SPECIFIC TESTS

• **Loss on Drying** ⟨731⟩

Analysis: Dry in vacuum at 60° for 2 h.

Acceptance criteria: NMT 0.5%

ADDITIONAL REQUIREMENTS

• **Packaging and Storage:** Preserve in well-closed, light-resistant containers. Store at 25°, excursions permitted between 15° and 30°.

Change to read:

• **USP Reference Standards** ⟨11⟩

USP Fentanyl Citrate RS

▲ USP Fentanyl Related Compound E RS

1-Phenethyl-*N*-phenylpiperidin-4-amine.

$C_{19}H_{24}N_2$ 280.41

USP Fentanyl Related Compound G RS

N-(1-Phenethylpiperidin-4-yl)-*N*-phenylacetamide.

$C_{21}H_{26}N_2O$ 322.44▲ (USP 1-May-2021)

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

Topic/Question	Contact	Expert Committee
FENTANYL CITRATE	Documentary Standards Support	SM22020 Small Molecules 2

Chromatographic Database Information: Chromatographic Database

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