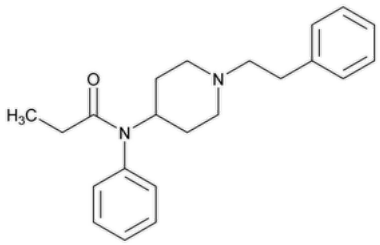
Status: Currently Official on 14-Feb-2025
Official Date: Official as of 01-Jan-2021
Document Type: USP Monographs
DocId: GUID-C0933C5C-368A-4492-BC41-930252AE330A_5_en-US
DOI: https://doi.org/10.31003/USPNF_M32760_05_01
DOI Ref: 37uvj

Fentanyl

Change to read:



$C_{22}H_{28}N_2O$ ▲336.48▲ (ERR 1-Jan-2021)

Propanamide, *N*-phenyl-*N*-[1-(2-phenylethyl)-4-piperidinyl];

N-(1-Phenethylpiperidin-4-yl)-*N*-phenylpropionamide CAS RN®: 437-38-7.

DEFINITION

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

[**Caution—**Great care should be taken to prevent inhaling particles of Fentanyl and skin exposure.]

IDENTIFICATION

- **A. Spectroscopic Identification Tests ⟨197⟩, *Infrared Spectroscopy*:** 197K or 197A
- **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

- **Procedure**

Solution A: Add 3 mL of triethylamine to about 950 mL of water in a 1000-mL volumetric flask. Adjust with perchloric acid to a pH of 2.62 ± 0.02, and dilute with water to volume.

Solution B: Acetonitrile

Diluent: *Solution A* and *Solution B* (9:1)

Mobile phase: See *Table 1*.

Table 1

Time (min)	Solution A (%)	Solution B (%)
0	90	10
2	90	10
3.5	85	15
5.1	82	18
7.6	72	28
11.5	63	37
15	40	60
19	40	60
20	90	10

Time (min)	Solution A (%)	Solution B (%)
25	90	10

System suitability stock solution: 0.1 mg/mL of USP Fentanyl Related Compound E RS prepared as follows. Transfer a suitable amount of USP Fentanyl Related Compound E RS to an adequate volumetric flask and dissolve in 50% of the final volume using acetonitrile. Dilute with water to volume.

Standard stock solution: 1 mg/mL of USP Fentanyl RS prepared by dissolving in a suitable volumetric flask 40% filled with acetonitrile and diluting with water to volume

Standard solution: 0.1 mg/mL of USP Fentanyl RS from the *Standard stock solution* in *Diluent*

System suitability solution: 0.3 µg/mL of USP Fentanyl Related Compound E RS and 0.1 mg/mL of USP Fentanyl RS prepared by diluting *System suitability stock solution* and *Standard stock solution* with *Diluent*

Sample stock solution: 1 mg/mL of Fentanyl prepared as follows. Transfer a suitable amount of Fentanyl to an adequate volumetric flask. Add 25% of final volume of acetonitrile, dissolve by shaking, and dilute with *Diluent* to volume.

Sample solution: 0.1 mg/mL of Fentanyl from the *Sample stock solution* in *Diluent*

Chromatographic system

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

Mode: LC

Detector: UV 206 nm

Column: 4.6-mm × 15-cm; 3.5-µm packing L7

Column temperature: 35°

Flow rate: 1 mL/min

Injection volume: 30 µL

System suitability

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

Suitability requirements

Resolution: NLT 1.2 between fentanyl and fentanyl related compound E peaks, *System suitability solution*

Tailing factor: 0.5–2.0, *Standard solution*

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

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of fentanyl ($C_{22}H_{28}N_2O$) in the portion of Fentanyl 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 RS in the *Standard solution* (mg/mL)

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

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

IMPURITIES

- **Residue on Ignition ⟨281⟩:** NMT 0.5%
- **Organic Impurities**

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

Solution A: Acetonitrile and 10 mM ammonium formate (5:95). Adjust with ammonium hydroxide to a pH of 9.5.

Solution B: Acetonitrile and 10 mM ammonium formate (95:5). Adjust with ammonium hydroxide to a pH of 9.5.

Mobile phase: See *Table 2*.

Table 2

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: 0.025% trifluoroacetic acid in a mixture of acetonitrile and water (5:95)

Sensitivity solution: 0.5 µg/mL of USP Fentanyl RS prepared as follows. Transfer a suitable amount of USP Fentanyl RS to an adequate volumetric flask. Dissolve in 10% of final volume using acetonitrile. Sonicate to dissolve, if necessary. Dilute with *Diluent* to volume.

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 amounts of USP Fentanyl Related Compound E RS and USP Fentanyl Related Compound G RS to an adequate volumetric flask. Dissolve in 10% of final volume using acetonitrile. Sonicate to dissolve, if necessary. Dilute with *Diluent* to volume.

Sample solution: 1.0 mg/mL of Fentanyl prepared as follows. Transfer a suitable amount of Fentanyl to an adequate volumetric flask. Dissolve in 10% of final volume using acetonitrile. Sonicate to dissolve, if necessary. Dilute with *Diluent* to volume.

Chromatographic system

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

Mode: LC

Detector: UV 240 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

Samples: *Sensitivity solution* and *Standard solution*

Suitability requirements

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 fentanyl related compound E in the portion of Fentanyl taken:

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

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 in the *Sample solution* (mg/mL)

Calculate the percentage of each other impurity in the portion of Fentanyl taken:

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

r_U = peak response of each other 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 in the *Sample solution* (mg/mL)

F = relative response factor (see *Table 3*)

Acceptance criteria: See *Table 3*. The reporting threshold is 0.05%.

Table 3

Name	Relative Retention Time	Relative Response Factor[a]	Acceptance Criteria, NMT (%)
Fentanyl *N*-oxide[b]	0.26	0.69	0.15
Fentanyl related compound G	0.78	1.0	0.15
Fentanyl pyruvyl analog[c]	0.92	3.0	0.15
Fentanyl	1.00	—	—
Fentanyl related compound E	1.14	—	0.15
Fentanyl butyryl analog[d]	1.21	1.5	0.15
Any unspecified impurity	—	1.0	0.10
Total impurities	—	—	0.50

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

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

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

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

SPECIFIC TESTS

• **Loss on Drying** ⟨731⟩

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

Acceptance criteria: NMT 0.5%

ADDITIONAL REQUIREMENTS

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

• **USP Reference Standards** ⟨11⟩

USP Fentanyl 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

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

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

Chromatographic Database Information: Chromatographic Database

Most Recently Appeared In:
Pharmacopeial Forum: Volume No. PF 44(1)

Current DocID: GUID-C0933C5C-368A-4492-BC41-930252AE330A_5_en-US

DOI: https://doi.org/10.31003/USPNF_M32760_05_01

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