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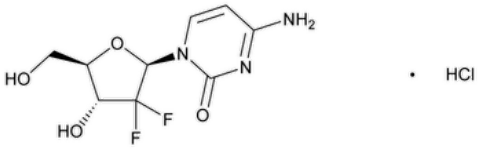
Gemcitabine Hydrochloride



$C_9H_{11}F_2N_3O_4 \cdot HCl$ 299.66

Cytidine, 2'-deoxy-2',2'-difluoro-, monohydrochloride;

2'-Deoxy-2',2'-difluorocytidine monohydrochloride (β-isomer) CAS RN®: 122111-03-9; UNII: U347PV74IL.

DEFINITION

Gemcitabine Hydrochloride contains NLT 97.5% and NMT 101.5% of gemcitabine hydrochloride ($C_9H_{11}F_2N_3O_4 \cdot HCl$), calculated on the as-is basis.

[**Caution—**Gemcitabine Hydrochloride is a potent cytotoxic agent. Great care should be taken to prevent inhaling particles and exposing the skin to it.]

IDENTIFICATION

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

Meets the requirements

• **B. Identification Tests—General ⟨191⟩, *Chemical Identification Tests, Chloride*:** Meets the requirements

• **C.** 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**

Mobile phase: 13.8 g of monobasic sodium phosphate and 2.5 mL of phosphoric acid in 1 L of water. [Note—The pH of this solution is 2.4–2.6.]

System suitability solution: Transfer 10 mg of Gemcitabine Hydrochloride to a small vial, add 4 mL of 168 mg/mL of potassium hydroxide in methanol, cap tightly, and sonicate. Heat at 55° for 6–16 h, allow to cool, and transfer the contents to a 100-mL volumetric flask with successive washes of 1% phosphoric acid. Dilute with 1% (v/v) phosphoric acid to volume. [Note—This solution contains about 0.02 mg/mL of gemcitabine α-anomer.]

Standard solution: 0.1 mg/mL of USP Gemcitabine Hydrochloride RS in water

Sample solution: 0.1 mg/mL of Gemcitabine Hydrochloride in water

Chromatographic system

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

Mode: LC

Detector: UV 275 nm

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

Flow rate: 1.2 mL/min

Injection volume: 20 µL

System suitability

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

[Note—The relative retention times for gemcitabine α-anomer and gemcitabine are about 0.5 and 1.0, respectively.]

Suitability requirements

Resolution: NLT 8.0 between gemcitabine α-anomer and gemcitabine, *System suitability solution*

Tailing factor: NMT 1.5 for the gemcitabine peak, *System suitability solution*

Relative standard deviation: NMT 1.0%, *Standard solution*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of gemcitabine hydrochloride ($C_9H_{11}F_2N_3O_4 \cdot HCl$) in the portion of Gemcitabine Hydrochloride 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 Gemcitabine Hydrochloride RS in the *Standard solution* (mg/mL)

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

Acceptance criteria: 97.5%–101.5% on the as-is basis

IMPURITIES

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

Change to read:

• **Organic Impurities**

System suitability solution and **Chromatographic system:** Proceed as directed in the *Assay*.

Solution A: Use the *Mobile phase*, prepared as directed in the *Assay*.

Solution B: Methanol

Mobile phase: See *Table 1*.

Table 1

Time (min)	Solution A (%)	Solution B (%)
0	97	3
8	97	3
13	50	50
20	50	50
25	97	3

Standard solution: 0.002 mg/mL each of USP Gemcitabine Hydrochloride RS and USP Cytosine RS in water

Sample solution: 2 mg/mL of Gemcitabine Hydrochloride in water

System suitability

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

Suitability requirements

Resolution: NLT 8.0 between gemcitabine α-anomer and gemcitabine, *System suitability solution*

Tailing factor: NMT 1.5 for the gemcitabine peak, *System suitability solution*

Relative standard deviation: NMT 2.0%, *Standard solution*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of cytosine in the portion of Gemcitabine Hydrochloride taken:

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

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

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

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

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

Calculate the percentage of each impurity other than cytosine in the portion of Gemcitabine Hydrochloride taken:

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

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

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

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

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

Acceptance criteria: See *Table 2*. The reporting threshold is 0.02%.

Table 2

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Cytosine▲ (ERR 1-Aug-2021)	0.4	0.1
Gemcitabine α-anomer[a]	0.7	0.1
Gemcitabine	1.0	—
Any individual unspecified impurity	—	0.1
Total impurities	—	0.2

[a] 4-Amino-1-(2-deoxy-2,2-difluoro-α-D-erythro-pentofuranosyl)-2(1*H*)-pyrimidinone.

SPECIFIC TESTS

• **Optical Rotation** ⟨781S⟩, *Procedures, Specific Rotation*

Sample solution: 10 mg/mL

Acceptance criteria: +43° to +50° at 20°

• **pH** ⟨791⟩

Sample solution: 10 mg/mL

Acceptance criteria: 2.0–3.0

• **Sterility Tests** ⟨71⟩, *Test for Sterility of the Product to Be Examined, Membrane Filtration*: Where the label states that Gemcitabine Hydrochloride is sterile, it meets the requirements.

• **Bacterial Endotoxins Test** ⟨85⟩: Where the label states that Gemcitabine Hydrochloride is sterile or must be subjected to further processing during the preparation of injectable dosage forms, it contains NMT 0.05 USP Endotoxin Units/mg of gemcitabine.

ADDITIONAL REQUIREMENTS

• **Packaging and Storage:** Preserve in tight containers.

• **Labeling:** Where it is intended for use in preparing injectable dosage forms, the label states that it is sterile or must be subjected to further processing during the preparation of injectable dosage forms.

Change to read:

• **USP Reference Standards** ⟨11⟩

USP Cytosine RS

▲Cytosine.▲ (ERR 1-Aug-2021)

$C_4H_5N_3O$ 111.10

USP Gemcitabine Hydrochloride RS

Topic/Question	Contact	Expert Committee
GEMCITABINE HYDROCHLORIDE	Documentary Standards Support	SM32020 Small Molecules 3

Chromatographic Database Information: Chromatographic Database

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