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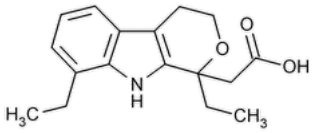
Etodolac

Change to read:



$C_{17}H_{21}NO_3$ ▲287.36▲ (USP 1-Dec-2024)

Pyrano[3,4-*b*]indole-1-acetic acid, 1,8-diethyl-1,3,4,9-tetrahydro-(±)-;

▲1,8-Diethyl-1,3,4,9-tetrahydropyrano[3,4-*b*]indol-1-ylacetic acid▲ (USP 1-Dec-2024) CAS RN®: 41340-25-4; UNII: 2M36281008.

DEFINITION

Etodolac contains NLT 98.0% and NMT 102.0% of etodolac ($C_{17}H_{21}NO_3$), calculated on the anhydrous basis.

IDENTIFICATION

Change to read:

• **A. Spectroscopic Identification Tests ⟨197⟩, *Infrared Spectroscopy*:** ▲197A or▲ (USP 1-Dec-2024) 197K

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-Dec-2024)

ASSAY

Change to read:

• **Procedure**

▲Protect solutions containing etodolac from light.

Solution A: 0.77 g/L of ammonium acetate in water

Solution B: Acetonitrile and *Solution A* (90:10)

Mobile phase: See *Table 1*. Return to the original conditions to re-equilibrate the system. [Note—A re-equilibration time of 5 min may be used.]

Table 1

Time (min)	Solution A (%)	Solution B (%)
0	80	20
18	58	42
18.1	0	100
20	0	100

Standard solution: 0.2 mg/mL of USP Etodolac RS in acetonitrile

Sample solution: 0.2 mg/mL of Etodolac in acetonitrile

Chromatographic system

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

Mode: LC

Detector: UV 225 nm

Column: 4.6-mm × 15-cm; 3.5-µm packing L26

Temperatures

Autosampler: 5°

Column: 35°

Flow rate: 1 mL/min

Injection volume: 5 µL

System suitability

Sample: *Standard solution*

Suitability requirements

Tailing factor: NMT 2.0

Relative standard deviation: NMT 0.73%

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of etodolac ($C_{17}H_{21}NO_3$) in the portion of Etodolac taken:

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

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

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

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

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

▲ (USP 1-Dec-2024)

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

IMPURITIES

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

• **Limit of Chloride**

Sample: 1.0 g of Etodolac

Titrimetric system

(See *Titrimetry ⟨541⟩*.)

Mode: Direct titration

Titrant: 0.01 N silver nitrate

Endpoint detection: Potentiometric

Analysis: Dissolve the *Sample* in 60 mL of methanol, dilute with 10 mL of water, and add 20 mL of 2 N nitric acid. Titrate with the *Titrant*.

Acceptance criteria: NMT 300 ppm

Delete the following:

▲• **Limit of Alcohol and Methanol**▲ (USP 1-Dec-2024)

Change to read:

• **Organic Impurities**

▲Protect solutions containing etodolac from light.

Solution A, Solution B, and **Chromatographic system:** Proceed as directed in the *Assay*.

Mobile phase: See *Table 2*. Return to the original conditions and re-equilibrate the system. [Note—A re-equilibration time of 15 min may be used.]

Table 2

Time (min)	Solution A (%)	Solution B (%)
0	80	20
25	50	50
50	50	50

System suitability solution: 1.0 mg/mL of USP Etodolac Peak Identification Mixture RS in acetonitrile. Sonicate to dissolve as needed.

Standard solution: 0.002 mg/mL of USP Etodolac RS in acetonitrile. Sonicate to dissolve as needed.

Sensitivity solution: 0.5 µg/mL of USP Etodolac RS in acetonitrile from the *Standard solution*

Sample solution: 1.0 mg/mL of Etodolac in acetonitrile. Sonicate to dissolve as needed.

System suitability

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

Suitability requirements

Resolution: NLT 3.0 between etodolac and 7-ethyltrypthanol (etodolac related compound H), *System suitability 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 Etodolac taken:

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

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

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

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

C_U = concentration of Etodolac 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	Acceptance Criteria, NMT (%)
8-Desethyl etodolac[a]	0.67	0.98	0.20
8-Methyl etodolac analog[b]	0.83	1.0	0.2
1-Methyl etodolac analog[c]	0.85	0.95	0.50
Etodolac	1.00	1.0	—
7-Ethyltrypthanol (etodolac related compound H)[d]	1.14	1.3	0.2
8-Isopropyl etodolac analog[e]	1.19	1.0	0.1
1-Propyl etodolac analog[f]	1.20	1.0	0.1
8-Propyl etodolac analog[g]	1.22	1.0	0.1
1-Isopropyl etodolac analog[h]	1.24	1.0	0.1
Etodolac dimer[i]	1.54	1.1	0.1
Etodolac methyl ester[j]	2.50	0.91	0.2
Any unspecified impurity	—	1.0	0.10
Total impurities	—	—	1.0

[a] 1-Ethyl-1,3,4,9-tetrahydropyrano[3,4-*b*]indol-1-ylacetic acid.

[b] 1-Ethyl-8-methyl-1,3,4,9-tetrahydropyrano[3,4-*b*]indol-1-ylacetic acid.

[c] 8-Ethyl-1-methyl-1,3,4,9-tetrahydropyrano[3,4-*b*]indol-1-ylacetic acid.

[d] 2-(7-Ethyl-1*H*-indol-3-yl)ethan-1-ol.

[e] 1-Ethyl-8-isopropyl-1,3,4,9-tetrahydropyrano[3,4-*b*]indol-1-ylacetic acid.

[f] 8-Ethyl-1-propyl-1,3,4,9-tetrahydropyrano[3,4-*b*]indol-1-ylacetic acid.

[g] 1-Ethyl-8-propyl-1,3,4,9-tetrahydropyrano[3,4-*b*]indol-1-ylacetic acid.

[h] 8-Ethyl-1-isopropyl-1,3,4,9-tetrahydropyrano[3,4-*b*]indol-1-ylacetic acid.

[i] 3-(7-Ethyl-1*H*-indol-3-yl)-3-[7-ethyl-3-(2-hydroxyethyl)-1*H*-indol-2-yl]pentanoic acid.

j Methyl 2-(1,8-diethyl-1,3,4,9-tetrahydropyrano[3,4-*b*]indol-1-yl)acetate.

▲ (USP 1-Dec-2024)

SPECIFIC TESTS

• **Water Determination** ⟨921⟩, *Method I*: NMT 0.5%

ADDITIONAL REQUIREMENTS

Change to read:

• **Packaging and Storage:** Preserve in tight containers.▲Store at controlled room temperature.▲ (USP 1-Dec-2024)

Change to read:

• **USP Reference Standards** ⟨11⟩

USP Etodolac RS

▲ USP Etodolac Peak Identification Mixture RS

It contains etodolac, 7-ethyltrypthanol (etodolac related compound H), and other impurities of etodolac.▲ (USP 1-Dec-2024)

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

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

Chromatographic Database Information: Chromatographic Database

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