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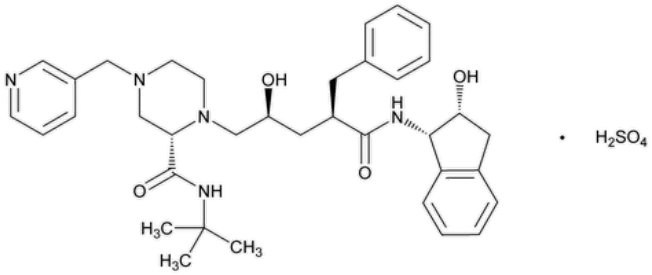
# Indinavir Sulfate



$C_{36}H_{47}N_5O_4 \cdot H_2SO_4$ 711.87

D-*erythro*-Pentonamide, 2,3,5-trideoxy-*N*-(2,3-dihydro-2-hydroxy-1*H*-inden-1-yl)-5-[2-[[(1,1-dimethylethyl)amino] carbonyl]-4-(3-pyridinylmethyl)-1-piperazinyl]-2-(phenylmethyl)-, [1(1*S*,2*R*),5(*S*)]-, sulfate (1:1) (salt);
(α*R*,γ*S*,2*S*)-α-Benzyl-2-(*tert*-butylcarbamoyl)-γ-hydroxy-*N*-[(1*S*,2*R*)-2-hydroxy-1-indanyl]-4-(3-pyridylmethyl)-1-piperazinevaleramide sulfate (1:1) (salt) CAS RN®: 157810-81-6; UNII: 771H53976Q.

## DEFINITION

Indinavir Sulfate contains NLT 98.5% and NMT 101.5% of $C_{36}H_{47}N_5O_4 \cdot H_2SO_4$, calculated on the anhydrous, solvent-free basis.

## IDENTIFICATION

***Change to read:***

- **A.** ▲**Spectroscopic Identification Tests ⟨197⟩, *Infrared Spectroscopy*: 197M**▲ (CN 1-May-2020) **:** Maxima at about 3.0–3.1, 5.9, 6.2, and 13.6 µm
- **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, *Sulfate*⟨191⟩:** Meets the requirements

**Sample solution:** A solution of 10 mg/mL in water

## ASSAY

- **Procedure**

**Solution A:** Dibutyl ammonium phosphate and water (1:50). Adjust with sodium hydroxide TS to a pH of 6.5 ± 0.5.

**Mobile phase:** Acetonitrile and *Solution A* (9:11)

**Standard solution:** 0.5 mg/mL of USP Indinavir RS in *Mobile phase*

**Sample solution:** 0.6 mg/mL of Indinavir Sulfate in *Mobile phase*

**Chromatographic system**

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

**Mode:** LC

**Detector:** UV 260 nm

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

**Column temperature:** 40°

**Flow rate:** 1 mL/min

**Injection size:** 10 µL

**System suitability**

**Sample:** *Standard solution*

**Suitability requirements**

**Column efficiency:** NLT 4000 theoretical plates

**Tailing factor:** Less than 2.0

**Relative standard deviation:** NMT 1.0%

**Analysis**

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

Calculate the percentage of $C_{36}H_{47}N_5O_4 \cdot H_2SO_4$ in the portion taken:

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

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

$r_S$ = peak response from the *Standard solution*

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

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

$M_{r1}$ = molecular weight of indinavir sulfate, 711.87

$M_{r2}$ = molecular weight of indinavir, 613.79

**Acceptance criteria:** 98.5%–101.5% on the anhydrous, solvent-free basis

## OTHER COMPONENTS

- **Procedure 1: Content of Sulfate**

**Solution A:** Methanol and formaldehyde (1000:0.3)

**Diluent:** *Solution A* and water (1:1)

**Sample solution:** 6.25 mg/mL of Indinavir Sulfate in *Diluent*

**Analysis:** Titrate with 0.1 M lead perchlorate VS, using a lead-specific electrode in conjunction with a suitable reference electrode. Each mL of 0.1 M lead perchlorate VS is equivalent to 9.604 mg of sulfate.

**Acceptance criteria:** 13.2%–14.4%, calculated on the anhydrous and solvent-free basis

- **Procedure 2: Content of Alcohol**

**Standard solution:** 0.001 mL/mL of dehydrated alcohol, in water. [Note—Dehydrated alcohol is at 20°.]

**Sample solution:** 4 mg/mL of Indinavir Sulfate in water

**Chromatographic system**

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

**Mode:** GC

**Detector:** Flame ionization

**Column:** 0.53-mm × 30-m capillary column with a 1.0-µm film of phase G16

**Temperature**

**Column:** 35°

**Injector:** 140°

**Detector:** 220°

[Note—At the end of each 5-min isothermal run, increase the oven temperature to 200° before adjusting the column temperature to 35° for the next injection.]

**Flow rate:** 10 mL/min

**Carrier gas:** Helium

**Injection size:** 0.1 µL

**System suitability**

**Sample:** *Standard solution*

**Suitability requirements**

**Relative standard deviation:** NMT 2.0%

**Analysis**

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

Calculate the percentage of alcohol in the portion of Indinavir Sulfate taken:

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

$r_U$ = peak area from the *Sample solution*

$r_S$ = peak area from the *Standard solution*

$C_S$ = concentration of dehydrated alcohol in the *Standard solution* (mL/mL)

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

D = density of alcohol at 20°, 790 mg/mL

**Acceptance criteria:** 5.0%–8.0%

## IMPURITIES

### Inorganic Impurities

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

### Organic Impurities

- **Procedure**

**Solution A:** 0.27 g/L of monobasic potassium phosphate and 1.395 g/L of dibasic potassium phosphate, in water

**Solution B:** Acetronitrile

**Mobile phase:** See the gradient table below.

| Time (min) | Solution A (%) | Solution B (%) |
|---|---|---|
| 0 | 80 | 20 |
| 40 | 30 | 70 |
| 45 | 30 | 70 |
| 47 | 80 | 20 |
| 52 | 80 | 20 |

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

**System suitability solution:** 0.4 mg/mL of USP Indinavir System Suitability RS in *Diluent*

**Sample solution:** 0.5 mg/mL of Indinavir Sulfate in *Diluent*

**Chromatographic system**

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

**Mode:** LC

**Detector:** UV 220 nm

**Column:** 4.6-mm × 25-cm; 5-µm packing L1

**Flow rate:** 1 mL/min

**Injection size:** 20 µL

**System suitability**

**Sample:** *System suitability solution*

**Suitability requirements**

**Resolution:** NLT 1.8 between indinavir and indinavir related compound C

**Tailing factor:** More than 0.95 and less than 2.0, determined from the indinavir peak

**Analysis**

**Sample:** *Sample solution*

Calculate the percentage of each impurity in the portion of Indinavir Sulfate taken:

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

$r_U$ = peak area response for each impurity

$r_T$ = sum of the responses of all the peaks

**Acceptance criteria**

**Individual impurities:** See *Impurity Table 1*.

**Total impurities:** NMT 0.5%

**Impurity Table 1**

| Name | Relative Retention Time | Acceptance Criteria, NMT (%) |
|---|---|---|
| *cis*-Aminoindanol[a] | 0.18 | 0.1 |
| Desnicotinyl indinavir[b] | 0.80 | 0.1 |
| *threo*-Indinavir[c] | 0.98 | 0.1 |
| Indinavir lactone[d] | 1.14 | 0.1 |
| Diindanyl indinavir[e] | 1.30 | 0.1 |

[a] (1*S*,2*R*)-1-Aminoindan-2-ol.

[b] (*S*)-1-{(2*S*,4*R*)-4-Benzyl-2-hydroxy-5-[(1*S*,2*R*)-2-hydroxyindan-1-ylamino]-5-oxopentyl}-*N*-*tert*-butylpiperazine-2-carboxamide.

[c] (*S*)-1-{(2*R*,4*R*)-4-Benzyl-2-hydroxy-5-[(1*S*,2*R*)-2-hydroxyindan-1-ylamino]-5-oxopentyl}-*N*-*tert*-butyl-4-(pyridin-3-ylmethyl)piperazine-2-carboxamide.

[d] (*S*)-1-{[(2*S*,4*R*)-4-Benzyl-5-oxotetrahydrofuran-2-yl]methyl}-*N*-*tert*-butyl-4-(pyridin-3-ylmethyl)piperazine-2-carboxamide.

[e] (2*R*,2′*R*,4*S*,4′*S*)-5,5′-[(*S*)-2-(*tert*-Butylcarbamoyl)piperazine-1,4-diyl]bis{2-benzyl-4-hydroxy-*N*-[(1*S*,2*R*)-2-hydroxy-2,3-dihydro-1*H*-inden-1-yl]pentanamide}.

## SPECIFIC TESTS

- **Optical Rotation,** *Specific Rotation* ⟨781S⟩**:** +122° to +129°, at 365 nm, determined on the anhydrous, solvent-free basis
  **Sample solution:** 10 mg/mL in water
- **Water Determination,** *Method I* ⟨921⟩**:** NMT 1.5%, using 0.25 g

## ADDITIONAL REQUIREMENTS

- **Packaging and Storage:** Preserve in tight containers, protected from moisture. Store at 25°, excursions permitted between 15° and 30°.
- **USP Reference Standards** ⟨11⟩
  USP Indinavir RS
  USP Indinavir System Suitability RS

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

| Topic/Question | Contact | Expert Committee |
|---|---|---|
| INDINAVIR SULFATE | Documentary Standards Support | SM12020 Small Molecules 1 |

**Chromatographic Database Information:** Chromatographic Database

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