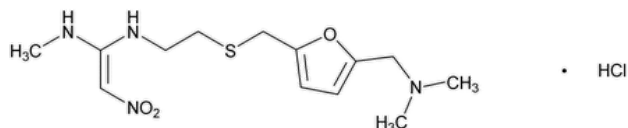


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Ranitidine Hydrochloride



$C_{13}H_{22}N_4O_3S \cdot HCl$ 350.86

1,1-Ethenediamine, *N*-[2-[[[5-[(dimethylamino)methyl]-2-furanyl]methyl]thio]ethyl]-*N'*-methyl-2-nitro-, monohydrochloride.

N-[2-[[[5-[(Dimethylamino)methyl]-2-furanyl]methyl]thio]ethyl]-*N'*-methyl-2-nitro-1,1-ethenediamine, hydrochloride CAS RN®: 66357-59-3; UNII: BK76465IHM.

» Ranitidine Hydrochloride contains not less than 97.5 percent and not more than 102.0 percent of $C_{13}H_{22}N_4O_3S \cdot HCl$, calculated on the dried basis.

Packaging and storage—Preserve in tight, light-resistant containers.

USP REFERENCE STANDARDS (11)—

[USP Ranitidine Hydrochloride RS](#)

[USP Ranitidine Resolution Mixture RS](#)

It is a mixture of ranitidine hydrochloride and four related impurities: ranitidine-*N*-oxide, ranitidine complex nitroacetamide, ranitidine diamine hemifumarate, and ranitidine amino alcohol hemifumarate.

Ranitidine-N-oxide: *N,N*-dimethyl[5-[[[2-[[1-(methylamino)-2-nitroethenyl]amino]ethyl]sulphanyl]methyl]furan-2-yl]methanamine *N*-oxide.

Ranitidine complex nitroacetamide: *N*-[2-[[[5-[(dimethyl amino)methyl]furan-2-yl]methyl]sulphanyl]ethyl]-2-nitroacetamide.

Ranitidine diamine hemifumarate (related compound A): 5-[[[(2-aminoethyl)thio]methyl]-*N,N*-dimethyl-2-furanmethanamine, hemifumarate salt.

Ranitidine amino alcohol hemifumarate: [5-[(dimethylamino)methyl]furan-2-yl]methanol.

Identification—

Change to read:

A: [▲Spectroscopic Identification Tests \(197\)](#), [Infrared Spectroscopy: 197M](#)▲ (CN 1-May-2020) .

Change to read:

B: [▲Spectroscopic Identification Tests \(197\)](#), [Ultraviolet-Visible Spectroscopy: 197U](#)▲ (CN 1-May-2020)

Solution: 10 µg per mL.

Medium: water.

Absorptivities at 229 nm and 315 nm, calculated on the dried basis, do not differ by more than 3.0%.

C: A solution of it meets the requirements of the tests for [Chloride \(191\)](#).

pH (791): between 4.5 and 6.0, in a solution (1 in 100).

LOSS ON DRYING (731)—Dry it in vacuum at 60° for 3 hours: it loses not more than 0.75% of its weight.

RESIDUE ON IGNITION (281): not more than 0.1%.

Chromatographic purity—

Diluent, Mobile phase, Resolution solution, and Chromatographic system—Proceed as directed in the Assay.

Standard solution—Prepare as directed for *Standard preparation* in the Assay.

Test solution—Prepare as directed for *Assay preparation* in the Assay.

Procedure—Separately inject equal volumes (about 10 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and identify the ranitidine peak and the peaks due to impurities and degradation products listed in the table below.

Name	Relative Retention Time
Ranitidine simple nitroacetamide ¹	0.14
Ranitidine oxime ²	0.21
Ranitidine amino alcohol ³	0.45
Ranitidine diamine ⁴	0.57
Ranitidine S-oxide ⁵	0.64
Ranitidine N-oxide ⁶	0.72
Ranitidine complex nitroacetamide ⁷	0.84
Ranitidine formaldehyde adduct ⁸	1.36
Ranitidine bis-compound ⁹	1.75

¹ N-Methyl-2-nitroacetamide.

² 3-(Methylamino)-5,6-dihydro-2H-1,4-thiazin-2-one oxime.

³ {5-[(Dimethylamino)methyl]furan-2-yl}methanol.

⁴ 5-[(2-Aminoethylthio)methyl]-N,N-dimethyl-2-furanmethanamine (ranitidine related compound A).

⁵ N-{2-[(5-[(Dimethylamino)methyl]-2-furanyl)methyl]sulfinyl}ethyl)-N'-methyl-2-nitro-1,1-ethenediamine (ranitidine related compound C).

⁶ N,N-Dimethyl(5-[(2-[(1-(methylamino)-2-nitroethenyl]amino)ethyl)sulphonyl]methyl)furan-2-yl)methanamine N-oxide.

⁷ N-{2-[(5-[(Dimethylamino)methyl]furan-2-yl)methyl]sulphonyl}ethyl)-2-nitroacetamide.

⁸ 2,2'-Methylenebis(N-{2-[(5-[(dimethylamino)methyl]furan-2-yl)methyl]sulphonyl}ethyl)-N'-methyl-2-nitroethene-1,1-diamine).

⁹ N,N'-bis{2-[(5-[(Dimethylamino)methyl]-2-furanyl)methyl]thio}ethyl}-2-nitro-1,1-ethenediamine (ranitidine related compound B).

Measure the responses for the major peaks, and calculate the percentage of each impurity in the portion of Ranitidine Hydrochloride taken by the formula:

$$100CV/W(r_i/r_s)$$

in which C is the concentration, in mg per mL, of ranitidine hydrochloride in the *Standard solution*; V is the volume, in mL, of the *Test solution*; W is the weight, in mg, of Ranitidine Hydrochloride taken to prepare the *Test solution*; r_i is the peak response for each impurity obtained from the *Test solution*; and r_s is the ranitidine peak response obtained from the *Standard solution*: not more than 0.3% of ranitidine bis-compound is found, not more than 0.1% of any other single impurity is found, and not more than 0.5% of total impurities is found. The reporting level for impurities is 0.05%.

Assay—

Phosphate buffer—Place approximately 1900 mL of water in a 2.0-L volumetric flask, accurately add 6.8 mL of phosphoric acid, and mix. Accurately add 8.6 mL of 50% sodium hydroxide solution, and dilute with water to volume. If necessary, adjust with 50% sodium hydroxide solution or phosphoric acid to a pH of 7.1, and filter.

Solution A—Prepare a mixture of *Phosphate buffer* and acetonitrile (98:2).

Solution B—Prepare a mixture of *Phosphate buffer* and acetonitrile (78:22).

Mobile phase—Use variable mixtures of *Solution A* and *Solution B* as directed for *Chromatographic system*. Make adjustments if necessary (see *System Suitability* under [Chromatography \(621\)](#)).

Diluent—Use *Solution A*.

Standard preparation—Dissolve an accurately weighed quantity of [USP Ranitidine Hydrochloride RS](#) in *Diluent* to obtain a solution having a known concentration of about 0.125 mg of ranitidine hydrochloride per mL.

Resolution solution—Transfer about 1.3 mg of [USP Ranitidine Resolution Mixture RS](#) to a 10-mL volumetric flask, and dissolve in and dilute with *Diluent* to volume.

[NOTE—[USP Ranitidine Resolution Mixture RS](#) contains ranitidine hydrochloride and four related impurities: ranitidine amino alcohol hemifumarate, ranitidine diamine hemifumarate, ranitidine *N*-oxide, and ranitidine complex nitroacetamide.]

Assay preparation—Transfer about 25 mg of Ranitidine Hydrochloride, accurately weighed, to a 200-mL volumetric flask. Dissolve in and dilute with *Diluent* to volume, and mix.

Chromatographic system (see [CHROMATOGRAPHY \(621\)](#))—The liquid chromatograph is equipped with a 230-nm detector and a 4.6-mm × 10-cm column containing 3.5-μm packing L1 that is stable from pH 1 to 12. The flow rate is about 1.5 mL per minute. The column temperature is maintained at 35°. The chromatograph is programmed as follows.

Time (minutes)	Solution A (%)	Solution B (%)	Elution
0–10	100→0	0→100	linear gradient
10–15	0	100	isocratic
15–16	0→100	100→0	linear gradient
16–20	100	0	re-equilibration

Chromatograph the *Resolution solution*, and identify the peaks using the table of impurities and degradation products (found above): the resolution, *R*, between the peaks for ranitidine *N*-oxide and ranitidine complex nitroacetamide is not less than 1.5. Chromatograph the *Standard preparation*, and record the peak responses as directed for *Procedure*: the relative standard deviation for replicate injections is not more than 1.0%.

Procedure—Separately inject equal volumes (about 10 μL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the areas for the major peaks. Calculate the percentage of C₁₃H₂₂N₄O₃S · HCl in the portion of Ranitidine Hydrochloride taken by the formula:

$$100(C_s/C_u)(r_u/r_s)$$

in which *C_s* and *C_u* are the concentrations, in mg per mL, of ranitidine hydrochloride in the *Standard preparation* and the *Assay preparation*, respectively; and *r_u* and *r_s* are the peak responses obtained from the *Assay preparation* and the *Standard preparation*, respectively.

Auxiliary Information - Please [check for your question in the FAQs](#) before contacting USP.

Topic/Question	Contact	Expert Committee
RANITIDINE HYDROCHLORIDE	Documentary Standards Support	SM32020 Small Molecules 3
REFERENCE STANDARD SUPPORT	RS Technical Services RSTECH@usp.org	SM32020 Small Molecules 3

Chromatographic Database Information: [Chromatographic Database](#)

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