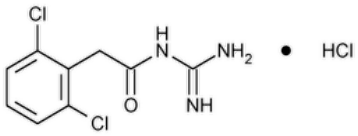
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Guanfacine Hydrochloride



$C_9H_9Cl_2N_3O \cdot HCl$ 282.55

Benzeneacetamide, *N*-(aminoiminomethyl)-2,6-dichloro-, monohydrochloride.

N-Amidino-2-(2,6-dichlorophenyl)acetamide monohydrochloride CAS RN®: 29110-48-3; UNII: PML56A160O.

» Guanfacine Hydrochloride contains not less than 98.0 percent and not more than 102.0 percent of $C_9H_9Cl_2N_3O \cdot HCl$, calculated on the dried basis. [**Caution—**Guanfacine Hydrochloride is a potent antihypertensive drug. Minimize flying dust, and avoid all bodily and respiratory contact with this substance.]

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

USP Reference Standards ⟨11⟩—

USP Guanfacine Hydrochloride RS

Identification—

Change to read:

A: ▲*Spectroscopic Identification Tests* ⟨197⟩*, Infrared Spectroscopy: 197K*▲ (CN 1-May-2020) ·

B: The retention time of the major peak in the chromatogram of the *Assay preparation* corresponds to that in the chromatogram of the *Standard preparation*, as obtained in the *Assay*.

Loss on drying ⟨731⟩—Dry it at 105° for 4 hours: it loses not more than 0.5% of its weight.

Residue on ignition ⟨281⟩**:** not more than 0.1%.

Related compounds—

Spray reagent—[Caution—Avoid contact with o-tolidine. Prepare and use this Spray reagent in a well-ventilated hood.] Dissolve 50 mg of *o*-tolidine in 100 mL of alcohol, and mix.

Chlorine chamber—Transfer 1.5 g of potassium permanganate to a 100-mL beaker, dissolve in and dilute with water to volume, and mix. Transfer 25 mL of this solution to a beaker, and place the beaker inside a chromatographic chamber. Pipet 10 mL of hydrochloric acid into the beaker, and cover the chamber.

Developing solvent system—Prepare a fresh mixture of ethyl acetate, glacial acetic acid, and acetonitrile (70:25:3).

Standard solutions—Dissolve accurately weighed quantities of USP Guanfacine Hydrochloride RS and guanidine hydrochloride in methanol to obtain a solution having a known concentration of 0.4 mg each of USP Guanfacine Hydrochloride RS and guanidine hydrochloride per mL. Quantitatively dilute this solution with methanol to obtain *Standard solutions* having the following compositions:

Standard Solution	Dilution	Concentration (µg RS and Guanidine Hydrochloride per mL)	Percentage (% for Comparison with Test Specimen)
1	(undiluted)	400	2.0
2	(1 in 2)	200	1.0
3	(1 in 4)	100	0.5
4	(1 in 8)	50	0.25

Test solution—Dissolve an accurately weighed quantity of Guanfacine Hydrochloride in methanol to obtain a solution having a concentration of about 20 mg per mL.

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Procedure—Use a thin-layer chromatographic plate (see *Chromatography ⟨621⟩* coated with a 0.25-mm layer of chromatographic silica gel. Prewash the plates by placing in a chromatographic chamber saturated with *Developing solvent system.* Remove the plates from the chamber, and allow to dry. Separately apply 10 µL each of the *Standard solutions* and the *Test solution* to the chromatographic plate. Allow the spots to dry, and develop the chromatogram in *Developing solvent* until the solvent front has moved about three-fourths of the length of the plate. Remove the plate from the chamber, mark the solvent front, and allow the plate to air-dry for about 1 hour. Examine the plate under short-wavelength UV light. Place the dried plate in the *Chlorine chamber* for 15 minutes, remove, and allow the excess chlorine to evaporate by air drying for 5 minutes. Spray the plate with *Spray reagent*, and examine: any spot due to guanidine hydrochloride observed in the chromatogram of the *Test solution* is not greater in size or intensity than the guanidine hydrochloride spot obtained from *Standard solution 3* (0.5%); no other individual impurity spot observed in the chromatogram of the *Test solution* is greater in size or intensity than the guanfacine hydrochloride spot obtained from *Standard solution 4* (0.25%); and the sum of all impurities found, including guanidine hydrochloride, is not more than 1.0%.

Chromatographic purity—

Spray reagent 1—Prepare a mixture of tertiary butyl alcohol and water (9:1).

Spray reagent 2—Dissolve 5 g of 4,4'-tetramethyldiaminodiphenylmethane in 20 mL of glacial acetic acid, add 10 mL of water, and mix (*Solution 1*). Dissolve 6 g of potassium iodide in 120 mL of water, and mix (*Solution 2*). Dissolve 0.3 g of ninhydrin in 10 mL of glacial acetic acid, dilute with water to 100 mL, and mix (*Solution 3*). Mix *Solution 1* and *Solution 2*, and add 9 mL of *Solution 3*.

Developing solvent system—Prepare a fresh mixture of hexanes, diisopropyl ether, toluene, and glacial acetic acid (60:30:5:3).

Reference solutions—Dissolve an accurately weighed quantity of 2,6-dichlorophenylacetic acid in a mixture of methanol and water (9:1) to obtain a solution having a concentration of 1 mg per mL (*Reference solution 1*). Quantitatively dilute this solution with a mixture of methanol and water (9:1) to obtain *Reference solution 2* and *Reference solution 3* having known concentrations of 0.5 and 0.25 mg per mL of 2,6-dichlorophenylacetic acid, respectively.

Test solution—Prepare a solution of Guanfacine Hydrochloride in a mixture of methanol and water (9:1), containing 100 mg per mL.

Procedure—Use a thin-layer chromatographic plate (see *Chromatography ⟨621⟩*) coated with a 0.25-mm layer of chromatographic silica gel. Prewash the plates by placing in a chromatographic chamber saturated with *Developing solvent system*. Remove the plates from the chamber, and allow to dry. Separately apply 25 µL of each of the *Reference solutions* and the *Test solution* to the chromatographic plate. Allow the spots to dry, and develop the chromatograms in the *Developing solvent system* until the solvent front has moved about three-fourths of the length of the plate. Remove the plate from the chamber, mark the solvent front, and allow the plate to air-dry for 30 minutes. Examine the plate under short-wavelength UV light. Spray the plate with *Spray reagent 1*, wait for 1 minute, and then spray with *Spray reagent 2*. Place the wet plate under short-wavelength UV light for 10 minutes, remove, and observe under white light: no spot observed in the chromatogram of the *Test solution*, other than that due to guanfacine hydrochloride, is greater in size or intensity than the principal spot obtained from *Reference solution 2* (0.5%); and the sum of all impurities found is not more than 1.0%.

Assay—

Dilute phosphoric acid—Prepare a mixture of water and phosphoric acid (4:1).

Buffer solution—Dissolve 68 g of monobasic potassium phosphate in water, dilute with water to 1000 mL, and mix. Dilute 100 mL of this solution with water to 1000 mL, add 5 mL of triethylamine, mix, and adjust with *Dilute phosphoric acid* to a pH of 3.0.

Mobile phase—Prepare a filtered and degassed mixture of *Buffer solution* and acetonitrile (79:21). Make adjustments if necessary (see *System Suitability* under *Chromatography ⟨621⟩*).

Standard preparation—Dissolve an accurately weighed quantity of USP Guanfacine Hydrochloride RS in a mixture of acetonitrile and water (3:1) to obtain a solution having a known concentration of about 1 mg of USP Guanfacine Hydrochloride RS per mL. Transfer 2.0 mL of this solution to a 50-mL volumetric flask, dilute with *Mobile phase* to volume, and mix.

Assay preparation—Transfer an accurately weighed quantity of about 50 mg of Guanfacine Hydrochloride to a 50-mL volumetric flask, dissolve in and dilute with a mixture of acetonitrile and water (3:1) to volume, and mix. Transfer 2.0 mL of this solution to a 50-mL volumetric flask, dilute with *Mobile phase* to volume, and mix.

Chromatographic system (see *Chromatography ⟨621⟩*)—The liquid chromatograph is equipped with a 220-nm detector and a 4.6-mm × 15-cm column that contains packing L1. The flow rate is about 1 mL per minute. Chromatograph the *Standard preparation*, and record the responses as directed for *Procedure:* the capacity factor, *k'*, is between 2 and 5; the column efficiency is not less than 1500 theoretical plates; the tailing factor is not more than 2; and the relative standard deviation for replicate injections is not more than 2.0%.

Procedure—Separately inject equal volumes (about 20 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 quantity, in mg, of $C_9H_9Cl_2N_3O \cdot HCl$ in the portion taken by the formula:

$$1.25C(r_U/r_S)$$

in which C is the concentration, in µg per mL, of USP Guanfacine Hydrochloride RS in the *Standard preparation;* and r_U and r_S are the guanfacine hydrochloride peaks obtained from the *Assay preparation* and the *Standard preparation*, respectively.

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