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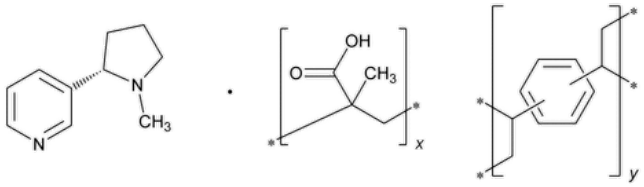
Nicotine Polacrilex



$[(C_4H_6O_2)_x(C_{10}H_{10})_y](C_{10}H_{14}N_2)$

2-Propenoic acid, 2-methyl-, polymer with diethenylbenzene, complex with (*S*)-3-(1-methyl-2-pyrrolidinyl)pyridine;

Methacrylic acid polymer with divinylbenzene, complex with nicotine CAS RN®: 96055-45-7.

DEFINITION

Nicotine Polacrilex is a weak carboxylic cation-exchange resin prepared from methacrylic acid and divinylbenzene, in complex with nicotine. It may contain glycerin. Glycerin-free Nicotine Polacrilex contains NLT 95.0% and NMT 115.0% of the labeled amount of nicotine ($C_{10}H_{14}N_2$), calculated on the dried basis. Glycerin-containing Nicotine Polacrilex contains NLT 95.0% and NMT 115.0% of the labeled amount of nicotine ($C_{10}H_{14}N_2$), calculated on the anhydrous basis.

[Note—Nicotine Polacrilex is also known as Nicotine Resinate.]

IDENTIFICATION

Change to read:

• **A.** ▲**Spectroscopic Identification Tests ⟨197⟩, *Infrared Spectroscopy (for Nicotine)*:** 197K or 197A▲ (CN 1-May-2020)

Sample: Transfer an amount of Nicotine Polacrilex equivalent to 100 mg of nicotine to a 100-mL glass-stoppered tube. Add 20 mL of 1 M ammonium hydroxide, 5 mL of 10 M sodium hydroxide, and 20 mL of *n*-hexane. Shake for 5 min, and allow the phases to separate. Transfer the upper hexane phase to an evaporating dish, and evaporate on a steam bath.

Standard: Use USP Nicotine Bitartrate Dihydrate RS, and prepare as directed for the *Sample*.

Acceptance criteria: Meets the requirements

Change to read:

• **B.** ▲**Spectroscopic Identification Tests ⟨197⟩, *Infrared Spectroscopy (for Polacrilex)*:** 197K or 197A▲ (CN 1-May-2020)

Standard: Transfer a portion of USP Polacrilex Resin RS, equivalent to the amount of Nicotine Polacrilex used to prepare the *Sample solution* in the *Assay*, to a glass-stoppered tube. Add 10 mL of 1 M ammonium hydroxide, shake for 10 min, and then centrifuge. Decant the ammonia solution from the residue, and wash the residue by shaking it with three 10-mL volumes of water, decanting the water phase after each shaking. Wash with 10 mL of 0.1 N hydrochloric acid, decant the liquid, and dry the residue at 105°.

Sample: Use the residue obtained from the *Sample solution* in the *Assay*. Decant the ammonia solution remaining from the residue, and wash the residue by shaking it with three 10-mL volumes of water, decanting the water phase after each shaking. Wash with 10 mL of 0.1 N hydrochloric acid, decant the liquid, and dry the residue at 105°.

Acceptance criteria: 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**

Solution A: Add 25 mL of 1 M acetic acid to 900 mL of water, and then add 6 mL of ammonium hydroxide. Adjust with either 2 M acetic acid or 2 M ammonium hydroxide to a pH of 10.0, and dilute with water to 1000 mL.

Solution B: Acetonitrile

Mobile phase: See *Table 1*. [NOTE—Re-equilibration time may be adjusted, if necessary.]

Table 1

Time (min)	Solution A (%)	Solution B (%)
0	100	0
3	100	0
3.01	95	5
28	74	26
32	60	40
33	100	0
35	100	0

System suitability solution: 1.5 mg/mL of USP Nicotine Bitartrate Dihydrate RS and 6 µg/mL of USP Nicotine Related Compound G RS in water

Standard solution: 1.8 mg/mL of USP Nicotine Bitartrate Dihydrate RS in water

Sample solution: Nominally 0.6 mg/mL of nicotine prepared as follows. Transfer an amount of Nicotine Polacrilex equivalent to 30 mg of nicotine to a glass-stoppered tube. Add 10.0 mL of 1 M ammonium hydroxide, shake vigorously for 10 min, and then centrifuge. Transfer 5.0 mL of the clear solution to a 25-mL volumetric flask, add 5 mL of 1 M acetic acid, and dilute with water to volume. Retain the residue from centrifugation for use in *Identification B*.

Chromatographic system

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

Mode: LC

Detector: UV 254 nm

Column: 4.6-mm × 15-cm; 5-µm packing L1

Flow rate: 1.0 mL/min

Injection volume: 20 µL

System suitability

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

[NOTE—See *Table 2* for the relative retention times.]

Suitability requirements

Resolution: NLT 2.5 between nicotine and nicotine related compound G, *System suitability solution*

Tailing factor: NMT 2.0 for nicotine, *System suitability solution*

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

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of nicotine ($C_{10}H_{14}N_2$) in the portion of Nicotine Polacrilex taken:

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

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

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

C_S = concentration of USP Nicotine Bitartrate Dihydrate RS on the anhydrous basis in the *Standard solution* (mg/mL)

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

M_{r1} = molecular weight of nicotine, 162.23

M_{r2} = molecular weight of anhydrous nicotine bitartrate, 462.41

Acceptance criteria:

Glycerin free: 95.0%–115.0% on the dried basis

Glycerin containing: 95.0%–115.0% on the anhydrous basis

PERFORMANCE TESTS

• **Nicotine Release**

Solution A: 9 mg/mL of sodium chloride in water

Sample stock solution: Transfer an amount of Nicotine Polacrilex equivalent to 4 mg of nicotine to a glass-stoppered tube, add 10.0 mL of *Solution A* that has been warmed to 37°, and shake by mechanical means for 10 min. Immediately pass the liquid through a dry filter paper, discarding the first milliliter of the filtrate.

Sample solution: Transfer 1.0 mL of the *Sample stock solution* to a 25-mL volumetric flask, and dilute with 0.1 N hydrochloric acid to volume.

Instrumental conditions

(See *Ultraviolet-Visible Spectroscopy ⟨857⟩*.)

Mode: UV

Analytical wavelengths: 236, 259, and 282 nm

Blank: 1.0 mL of *Solution A* diluted with 0.1 N hydrochloric acid to 25 mL

Analysis

Samples: *Sample solution* and *Blank*

Calculate the percentage of nicotine ($C_{10}H_{14}N_2$) released:

$$\text{Result} = (A_{259} - 0.5A_{236} - 0.5A_{282}) \times (V/E) \times (F/W) \times (1/P) \times 100$$

A_{259} = absorbance of the *Sample solution*, corrected for the *Blank* absorbance, at a wavelength of 259 nm

A_{236} = absorbance of the *Sample solution*, corrected for the *Blank* absorbance, at a wavelength of 236 nm

A_{282} = absorbance of the *Sample solution*, corrected for the *Blank* absorbance, at a wavelength of 282 nm

V = dilution volume, 250 mL

E = specific absorbance of nicotine at a wavelength of 259 nm, 323 mL g^{-1} cm^{-1}

F = unit conversion factor, 1000 mg/g

W = weight of Nicotine Polacrilex (mg)

P = percentage of nicotine in Nicotine Polacrilex determined in the *Assay*

Acceptance criteria: NLT 70% in 10 min

IMPURITIES

• **Organic Impurities**

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

System suitability solution: 1.5 mg/mL of USP Nicotine Bitartrate Dihydrate RS and 6 µg/mL each of USP Nicotine Related Compound A RS, USP Nicotine Related Compound B RS, USP Nicotine Related Compound C RS, USP Nicotine Related Compound D RS, USP Nicotine Related Compound E RS, USP Nicotine Related Compound F RS, and USP Nicotine Related Compound G RS in water. [Note—The concentration of each related compound is in terms of the free base.]

Standard solution: 1.8 µg/mL of USP Nicotine Bitartrate Dihydrate RS in water

Sensitivity solution: 0.9 µg/mL of USP Nicotine Bitartrate Dihydrate RS in water from the *Standard solution*

System suitability

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

[Note—See *Table 2* for the relative retention times.]

Suitability requirements

Resolution: NLT 2.5 between nicotine and nicotine related compound G, *System suitability solution*

Tailing factor: NMT 2.0 for nicotine, *System suitability solution*

Relative standard deviation: NMT 5.0%, *Standard solution*

Signal-to-noise ratio: NLT 10, *Sensitivity solution*

Analysis

Samples: *Sample solution* and *Standard solution*

Calculate the percentage of each impurity in the portion of Nicotine Polacrilex taken:

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

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

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

C_S = concentration of USP Nicotine Bitartrate Dihydrate RS on the anhydrous basis in the *Standard solution* (mg/mL)

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

M_{r1} = molecular weight of nicotine, 162.23

M_{r2} = molecular weight of anhydrous nicotine bitartrate, 462.41

Acceptance criteria: See *Table 2*. The reporting threshold is 0.05%.

Table 2

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Nicotine related compound E	0.3	0.3
Nicotine related compound C	0.55	0.3
Nicotine related compound F	0.7	0.3
Nicotine related compound A	0.8	0.3
Nicotine related compound D	0.86	0.3
Nicotine related compound G	0.9	0.3
Nicotine	1.00	—
Nicotine related compound B	1.6	0.3
Any other unspecified impurity	—	0.10
Total impurities	—	0.8

SPECIFIC TESTS

- ***Water Determination*** ⟨921⟩**,** *Method I* (for glycerin-containing Nicotine Polacrilex)

  Sample solution: Transfer about 1.0 g of Nicotine Polacrilex to a 50-mL glass-stoppered test tube, and add 20.0 mL of methanol. Shake for 30 min, and allow to stand for 30 min. Use a 10-mL portion of the methanol layer for the titration.

  Acceptance criteria: NMT 5.0%

- **Loss on Drying** ⟨731⟩ (for glycerin-free Nicotine Polacrilex)

  Analysis: Dry at 105° for 2 h.

  Acceptance criteria: NMT 7.0%

ADDITIONAL REQUIREMENTS

- **Packaging and Storage:** Preserve in tight containers, protected from light.
- **Labeling:** Label to indicate if the article contains glycerin.
- **USP Reference Standards** ⟨11⟩

  USP Nicotine Bitartrate Dihydrate RS

  USP Nicotine Related Compound A RS

  Anatabine;
  1,2,3,6-Tetrahydro-2,3'-bipyridine.
  $C_{10}H_{12}N_2$ 160.22

USP Nicotine Related Compound B RS
3-(1-Methyl-1*H*-pyrrol-2-yl)pyridine; Also known as Nicotyrine.
$C_{10}H_{10}N_2$ 158.20

USP Nicotine Related Compound C RS
(*S*)-1-Methyl-5-(pyridin-3-yl)pyrrolidin-2-one; Also known as Cotinine.
$C_{10}H_{12}N_2O$ 176.22

USP Nicotine Related Compound D RS
3-(4,5-Dihydro-3*H*-pyrrol-2-yl)pyridine fumarate; Also known as Myosamine.
$C_9H_{10}N_2 \cdot C_4H_4O_4$ 262.26

USP Nicotine Related Compound E RS
(1*RS*,2*S*)-1-Methyl-2-(pyridin-3-yl)pyrrolidine 1-oxide oxalate; Also known as Nicotine *N*-oxide.
$C_{10}H_{14}N_2O \cdot C_2H_2O_4$ 268.27

USP Nicotine Related Compound F RS
3-(Pyrrolidin-2-yl)pyridine; Also known as Nornicotine.
$C_9H_{12}N_2$ 148.20

USP Nicotine Related Compound G RS
(*S*)-3-(Piperidin-2-yl)pyridine; Also known as Anabasine.
$C_{10}H_{14}N_2$ 162.23

USP Polacrilex Resin RS

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

Topic/Question	Contact	Expert Committee
NICOTINE POLACRILEX	Documentary Standards Support	SM42020 Small Molecules 4
REFERENCE STANDARD SUPPORT	RS Technical Services RSTECH@usp.org	SM42020 Small Molecules 4

Chromatographic Database Information: Chromatographic Database

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