Nicotine Polacrilex

Type of Posting	Revision Bulletin, Postponement
Posting Date	28–April–2017
Official Date	01–May–2017
Expert Committee	Chemical Medicines Monographs 4
Reason for Revision	Compliance

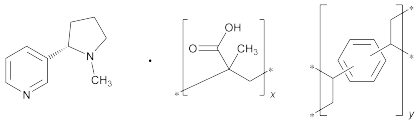
In accordance with the Rules and Procedures of the 2015-2020 Council of Experts, the Chemical Medicines Monographs 4 Expert Committee has revised the Nicotine Polacrilex.

The purpose for the revision is to postpone the deletion of *Water Determination, Method I* ⟨921⟩ and the addition of *Loss on Drying* <731>. A future revision to use a flexible monograph approach using different procedures for glycerin containing and glycerin free Nicotine Polacrilex is being considered.

The Nicotine Polacrilex Revision Bulletin supersedes the monograph becoming official in *USP 40–NF 35*.

Should you have any questions, please contact Gerald Hsu, Ph.D., Senior Scientific Liaison, (240-221-3097 or gdh@usp.org)

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 [96055-45-7].

DEFINITION

Change to read:

Nicotine Polacrilex is a weak carboxylic cation-exchange resin prepared from methacrylic acid and divinylbenzene, in complex with nicotine. It contains NLT 95.0% and NMT 115.0% of the labeled amount of nicotine ($C_{10}H_{14}N_2$), calculated on the •anhydrous• (RB 1-May-2017) basis.
▲[NOTE—Nicotine Polacrilex is also known as Nicotine Resinate.]▲*USP40*

IDENTIFICATION

Change to read:

- **A. INFRARED ABSORPTION ▲⟨197⟩ FOR NICOTINE:** [NOTE—Methods described in ⟨197K⟩ or ⟨197A⟩ may be used.]▲*USP40*
  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. INFRARED ABSORPTION ▲⟨197⟩ FOR POLACRILEX:** [NOTE—Methods described in ⟨197K⟩ or ⟨197A⟩ may be used.]▲*USP40*
  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, 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

Change to read:

- **PROCEDURE**
  Solution A: Add 25 mL of 1 M acetic acid to 900 mL of water, 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

▲*USP40*
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, 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 2.0%, *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: 95.0%–115.0% on the •anhydrous• (RB 1-May-2017) basis

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*. Disregard peaks that are less than 0.05% of the nicotine peak.

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

Change to read:

• **WATER DETERMINATION,** *Method I* ⟨**921**⟩
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%
•(Deletion of the *Water Determination* test is postponed indefinitely.)• (RB 1-May-2017)

Change to read:

▲• **LOSS ON DRYING** ⟨**731**⟩
Analysis: Dry at 105° for 2 h.
Acceptance criteria: NMT 7.0%
•(Postponed indefinitely)• (RB 1-May-2017)
▲*USP40*

Change to read:

• **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 mL 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⟩.)▲*USP40*
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 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} ▲*USP40*
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

ADDITIONAL REQUIREMENTS

Change to read:

• **PACKAGING AND STORAGE:** Preserve in tight containers, ▲protected from light.▲*USP40*

Change to read:

• **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
Nicotyrine;
3-(1-Methyl-1*H*-pyrrol-2-yl)pyridine.
$C_{10}H_{10}N_2$ 158.20
USP Nicotine Related Compound C RS
Cotinine;
(*S*)-1-Methyl-5-(pyridin-3-yl)pyrrolidin-2-one.
$C_{10}H_{12}N_2O$ 176.22
USP Nicotine Related Compound D RS
Myosmine;
3-(4,5-Dihydro-3*H*-pyrrol-2-yl)pyridine fumarate.
$C_9H_{10}N_2 \cdot C_4H_4O_4$ 262.26
USP Nicotine Related Compound E RS
Nicotine *N*-oxide;
(1*RS*,2*S*)-1-Methyl-2-(pyridin-3-yl)pyrrolidine 1-oxide oxalate.
$C_{10}H_{14}N_2O \cdot C_2H_2O_4$ 268.27
USP Nicotine Related Compound F RS
Nornicotine;
3-(Pyrrolidin-2-yl)pyridine.
$C_9H_{12}N_2$ 148.20
USP Nicotine Related Compound G RS
Anabasine;
(*S*)-3-(Piperidin-2-yl)pyridine.
$C_{10}H_{14}N_2$ 162.23
•USP Polacrilex Resin RS• (ERR 1-Jun-2016)