Nicotine Transdermal System

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In accordance with the Rules and Procedures of the Council of Experts, the Small Molecules 4 Expert Committee has revised the Nicotine Transdermal System monograph. The purpose for the revision is to increase the following *Acceptance criteria* in the *Organic Impurities* test to accommodate FDA-approved drug products.

Name	**Acceptance criteria, NMT (%)**		
	7 mg/24 h	**14 mg/24 h**	**21 mg/24 h**
Nicotine related compound E (1*R*,2*S* isomer)	Increase from **0.5** for all product strengths to:		
	1.4	**0.6**	**0.9**
Nicotine related compound E (1*S*,2*S* isomer)	Increase from **0.5** for all product strengths to:		
	1.4	**0.6**	**0.9**

The Nicotine Transdermal Systems Revision Bulletin supersedes the currently official monograph.

Should you have any questions, please contact Nicholas Garito, Sr. Scientific Liaison (301-816-8321 or njg@usp.org).

Revision Bulletin
Official: January 1, 2021

Nicotine Transdermal System

DEFINITION

Nicotine Transdermal System contains NLT 85% and NMT 115% of the labeled amount of nicotine ($C_{10}H_{14}N_2$).

IDENTIFICATION

• **A.** The retention time of the major peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay*.

• **B.** The UV spectrum of the major peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay*.

ASSAY

• **Procedure**

Solution A: Dissolve 1.1 g of monobasic potassium phosphate and 7.3 g of dibasic potassium phosphate in 1 L of water. [Note—The pH of this solution is between 7.5 and 7.6.]

Solution B: Methanol

Mobile phase: See *Table 1*.

Table 1

Time (min)	Solution A (%)	Solution B (%)
0	95	5
20	52.5	47.5
20.1	95	5
25	95	5

Extraction solvent: Methanol and tetrahydrofuran (90:10)

Standard stock solution: 3.0 mg/mL of USP Nicotine Bitartrate Dihydrate RS on the anhydrous basis (equivalent to about 1 mg/mL of nicotine) in *Extraction solvent*

Standard solution: 0.15 mg/mL of USP Nicotine Bitartrate Dihydrate RS on the anhydrous basis (equivalent to about 0.05 mg/mL of nicotine) in *Solution A* from the *Standard stock solution*

System suitability stock solution: 1 mg/mL each of USP Nicotine Related Compound E RS and USP Nicotine Related Compound D RS in *Extraction solvent*

System suitability solution: 0.15 mg/mL of USP Nicotine Bitartrate Dihydrate RS on the anhydrous basis and 0.1 mg/mL each of USP Nicotine Related Compound D RS and USP Nicotine Related Compound E RS in *Solution A* from the *Standard stock solution* and the *System suitability stock solution*

Sample stock solution: Nominally 1 mg/mL of nicotine from NLT 10 Transdermal System units prepared as follows. Transfer the required number of units to a suitable flask carefully ensuring that no adhesive contacts the walls. Add a suitable volume of *Extraction solvent.* Stopper the flask and seal to minimize the loss of the *Extraction solvent*. Shake the flask using a suitable shaker for 2 h.

Sample solution: Nominally 0.05 mg/mL of nicotine in *Solution A* from the *Sample stock solution*. Pass the solution through a suitable filter of 0.45-µm pore size.

Alternative sample preparation: If necessary, the *Sample stock solution* and the *Sample solution* may be prepared using the following alternative procedure.

Sample stock solution: Transfer one Transdermal System without the liner to a suitable 100-mL centrifuge tube with stopper. [NOTE—Cut Transdermal Systems larger than 2.5 cm^2 into 3–5-mm strips.] Add 10 mL of methylene chloride and a stirrer bar. Stopper the flask and stir the contents for NLT 4 h at room temperature. [NOTE—500 rpm for stirring speed is suitable.] Add 50 mL of 0.5% (v/v) phosphoric acid solution and continue extraction for another 1 h. Centrifuge at about 1000 rpm for NLT 5 min. Prepare separately the required number of extracts from the required number of Transdermal Systems following the same procedure described above. Combine equal volumes of the aqueous layer from each extract to obtain the *Sample stock solution*.

Sample solution: Nominally 0.03–0.05 mg/mL of nicotine from a suitable volume of the *Sample stock solution* and water

Chromatographic system

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

Mode: LC

Detector: UV 260 nm

Column: 4.6-mm × 15-cm; 3.5-µm packing L1

Column temperature: 45 ± 2°

Flow rate: 1.0 mL/min

Injection volume: 80 µL

System suitability

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

Suitability requirements

Resolution: NLT 1.5 between nicotine related compound D and 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 Transdermal System 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: 85%–115%

PERFORMANCE TESTS

- **DRUG RELEASE ⟨724⟩**

Test 1: If the product complies with this test, the labeling indicates that it meets USP *Drug Release Test 1*.

Medium: Phosphoric acid solution (1 in 1000); 250 mL, in a tall-form beaker

Apparatus 7: Proceed as directed in the chapter, using the transdermal system holder–cylinder (see *Drug Release ⟨724⟩*, *Figure 5b*).

Sample solution: Center the Transdermal System onto a dry, unused 10-cm × 10-cm piece of Cuprophan dialysis membrane with the adhesive side against the membrane, taking care to eliminate air bubbles between the membrane and the release surface. Attach the membrane to the cylinder using two Parker O-rings, such that one of the borders of the Transdermal System is aligned to the groove and it is wrapped around the cylinder. The filled beakers are weighed and pre-equilibrated to 32.0 ± 0.3°, before immersing the test sample. Reciprocate at a frequency of about 30 cycles/min with an amplitude of 2.0 ± 0.1 cm. At the end of each time interval, transfer the test sample to a fresh beaker containing the appropriate volume of *Medium*, weighed and pre-equilibrated to 32.0 ± 0.3°. At the end of each release interval, allow the beakers to cool to room temperature, make up for evaporative losses by adding water to obtain the original weight, and mix.

Times: 2, 12, and 24 h

Mobile phase: Transfer 0.2 mL of *N,N*-dimethyloctylamine to a 1-L volumetric flask, add 220 mL of acetonitrile, and mix. Add 300 mL of water, 0.2 mL of glacial acetic acid, 0.20 g of anhydrous sodium acetate, and 0.55 g of sodium 1-dodecanesulfonate, and dilute with water to volume. Mix for 1 h until clear. [Note—Equilibration of the column may take as long as 3 h.]

Standard solution: 0.15 mg/mL of USP Nicotine Bitartrate Dihydrate RS on the anhydrous basis (or 0.05 mg/mL of nicotine as free base) in *Medium*

System suitability solution: Transfer an amount of USP Nicotine Bitartrate Dihydrate RS equivalent to about 8 mg of nicotine to a 100-mL volumetric flask, and dissolve in 10 mL of acetonitrile. Add 5 mL of 30% hydrogen peroxide, and allow 15 min to react. Dilute with *Medium* to volume, and mix. Transfer 20 mL of this solution to a 100-mL volumetric flask, and dilute with *Standard solution* to volume.

Chromatographic system

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

Mode: LC

Detector: UV 254 nm

Column: 4.6-mm × 15-cm; packing L1

Flow rate: 1 mL/min

Injection volume: 50 µL

System suitability

Sample: *System suitability solution*

Suitability requirements

Resolution: NLT 1.1 between nicotine and any degradation peaks

Tailing factor: NMT 2.0

Relative standard deviation: NMT 1.5%

Analysis

Samples: *Standard solution* and *Sample solution*

Tolerances: See *Table 2*.

Table 2

Time (h)	Amount Released (%)
0–2	31–87
2–12	62–191
12–24	85–261

The percentages of the labeled amount of nicotine ($C_{10}H_{14}N_2$) released at the times specified, conform to *Acceptance Table 1*.

Test 2: If the product complies with this test, the labeling indicates that it meets USP *Drug Release Test 2*.

Buffer: 8 g/L of sodium chloride, 0.2 g/L of potassium chloride, 1.7 g/L of dibasic sodium phosphate, and 0.2 g/L of monobasic potassium phosphate in water

Medium: *Buffer*; 500 mL

Apparatus 6: 50 rpm, double-sided tape being used to attach the Transdermal System to the cylinder

Times: 6 and 24 h

Mobile phase: Acetonitrile, triethylamine, and water (300:1:700)

Standard solution: 0.6 mg/mL of USP Nicotine Bitartrate Dihydrate RS on the anhydrous basis (equivalent to about 0.2 mg/mL of nicotine) in *Medium*

Sample solution: At each of the test times, withdraw a 2-mL aliquot of the solution under test. Replace the aliquots withdrawn for analysis with fresh portions of *Medium*.

Chromatographic system

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

Mode: LC

Detector: UV 260 nm

Column: 4.6-mm × 12.5-cm; packing L1

Flow rate: 1 mL/min

Injection volume: 100 µL

System suitability

Sample: *Standard solution*

Suitability requirements

Tailing factor: NMT 2.0

Relative standard deviation: NMT 2.0%

Analysis

Samples: *Standard solution* and *Sample solution*

Tolerances: See *Table 3*.

Table 3

Time (h)	Amount Released (%)
6	71–157
24	156–224

The percentages of the labeled amount of nicotine ($C_{10}H_{14}N_2$) released at the times specified, conform to *Acceptance Table 1*.

Test 3: If the product complies with this test, the labeling indicates that it meets USP *Drug Release Test 3*.

Medium: Water; 900 mL

Apparatus 5: 50 rpm, the stainless steel disk assembly being replaced with a 5-cm watch glass for an 11-mg Transdermal System and an 8-cm watch glass for a 22-mg Transdermal System

Times: 1, 2, and 4 h

Standard solution: USP Nicotine Bitartrate Dihydrate RS in water having a known concentration of nicotine similar to that of the *Sample solution*.

Sample solution: At the specified times, withdraw a suitable volume of the solution under test.

Instrumental conditions

Mode: UV

Analytical wavelength: 259 nm

Blank: Water

Analysis

Samples: *Standard solution* and *Sample solution*

Tolerances: See *Table 4*.

Table 4

Time (h)	Amount Released (%)
1	35–75
2	55–95
4	NLT 73

The percentages of the labeled amount of nicotine ($C_{10}H_{14}N_2$) released at the times specified, conform to *Table 5*.

Table 5

Level	Tested	Criteria
L_1	6	No individual value lies outside each of the stated ranges and no individual value is less than the stated amount at the final test time.
L_2	6	The average value of the 12 units ($L_1 + L_2$) lies within each of the stated ranges and is NLT the stated amount at the final test time; none is more than 5% of the labeled content outside each of the stated ranges; and none is more than 5% of the labeled content below the stated amount at the final test time.
L_3	12	The average value of the 24 units ($L_1 + L_2 + L_3$) lies within each of the stated ranges and is NLT the stated amount at the final test time; NMT 2 of the 24 units are more than 5% of labeled content outside each of the stated ranges; NMT 2 of the 24 units are more than 5% of the labeled content below the stated amount at the final test time; and none of the units is more than 10% of the labeled content outside each of the stated ranges or more than 10% of the labeled content below the stated amount at the final test time.

Test 4: If the product complies with this test, the labeling indicates that it meets USP *Drug Release Test 4*.

Medium: 0.025 N hydrochloric acid; 600 mL

Apparatus 5: 50 rpm, a convex screen being used to hold the Transdermal System in position during testing

Times: 4 and 16 h

Standard solution: USP Nicotine Bitartrate Dihydrate RS in water having a known concentration of nicotine similar to that of the *Sample solution*

Sample solution: At the specified times, withdraw a suitable volume of the solution under test.

Instrumental conditions

Mode: UV

Analytical wavelength: 259 nm

Blank: Water

Analysis

Samples: *Standard solution* and *Sample solution*

Tolerances: See *Table 6*.

Table 6

Time (h)	Amount Released (%)
4	36–66
16	72–112

The percentages of the labeled amount of nicotine ($C_{10}H_{14}N_2$) released at the times specified, conform to *Acceptance Table 1*.

Test 5: If the product complies with this test, the labeling indicates that it meets USP *Drug Release Test 5*.

Buffer, Medium, and **Apparatus 6:** Proceed as directed in *Test 2*.

Times: 3, 6, and 24 h

Mobile phase, Standard solution, Sample solution, Chromatographic system, System suitability, and **Analysis:** Proceed as directed in *Test 2*, except to use an *Injection volume* of 30 µL.

Tolerances: See *Table 7*.

Table 7

Time (h)	Amount Released (%)
3	79–112
6	108–141
24	156–202

The percentages of the labeled amount of nicotine ($C_{10}H_{14}N_2$) released at the times specified, conform to *Acceptance Table 1*.

- **Uniformity of Dosage Units ⟨905⟩:** Meets the requirements

IMPURITIES

Change to read:

- **Organic Impurities**

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

Diluent: Tetrahydrofuran, methanol, and *Solution A* (0.5: 4.5: 95)

Sensitivity solution: 0.15 µg/mL of USP Nicotine Bitartrate Dihydrate RS (equivalent to about 0.05 µg/mL of nicotine) in *Diluent* from the *Standard solution*

System suitability

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

[NOTE—See *Table 8* for the relative retention times. The 1*R*,2*S* isomer of nicotine related compound E is a small peak that precedes the 1*S*,2*S* isomer, which is the major peak.]

Suitability requirements

Resolution: NLT 3 between nicotine related compound D and nicotine, *System suitability solution*; NLT 1.2 between the (1*R*,2*S*) and (1*S*,2*S*) isomers of nicotine related compound E, *System suitability solution*

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

Analysis

Sample: *Sample solution*

Calculate the percentage of each impurity in the portion of Transdermal System taken:

$$\text{Result} = (r_U/r_T) \times (1/F) \times 100$$

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

r_T = sum of all the peak responses from the *Sample solution*

F = relative response factor (see *Table 8*)

Acceptance criteria: See *Table 8*. Disregard peaks that are less than 0.05% of the nicotine peak.

Table 8

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)		
			7 mg/24 h	14 mg/24 h	21 mg/24 h
Nicotinic acid[a]	0.15	1.3	0.5	0.5	0.5
Nicotine related compound E (1*R*,2*S* isomer)	0.25	0.76	▲1.4▲ (RB 1-Jan-2021)	▲0.6▲ (RB 1-Jan-2021)	▲0.9▲ (RB 1-Jan-2021)
Nicotine related compound E (1*S*,2*S* isomer)	0.27	0.76	▲1.4▲ (RB 1-Jan-2021)	▲0.6▲ (RB 1-Jan-2021)	▲0.9▲ (RB 1-Jan-2021)
Nicotine related compound F[b, c]	0.38	—	—	—	—
Nicotine related compound C[d]	0.54	1.0	2.8	2.6	1.8
Nicotine related compound G[b, e]	0.64	—	—	—	—
Nicotine related compound A[b, f]	0.74	—	—	—	—

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)		
			7 mg/24 h	14 mg/24 h	21 mg/24 h
Nicotine related compound D	0.85	1.6	5.6	3.2	2.6
Nicotine	1.00	—	—	—	—
Nicotine related compound B[g]	1.19	1.9	0.5	0.5	0.5
Any other unspecified impurity	—	1.0	0.6	0.5	0.5
Total impurities	—	—	8.3	5.8	4.4

[a] 3-Pyridine carboxylic acid.

[b] Process impurity; controlled in drug substance and not to be included in total impurities.

[c] (*S*)-3-(Pyrrolidin-2-yl)pyridine; also known as nornicotine.

[d] (*S*)-1-Methyl-5-(pyridin-3-yl)pyrrolidin-2-one; also known as cotinine.

[e] (*S*)-3-(Piperidin-2-yl)pyridine; also known as anabasine.

[f] (*S*)-1,2,3,6-Tetrahydro-2,3'-bipyridine; also known as anatabine.

[g] 3-(1-Methyl-1*H*-pyrrol-2-yl)pyridine; also known as nicotyrine.

ADDITIONAL REQUIREMENTS

- **Packaging and Storage:** Preserve in the hermetic, light-resistant, unit-dose pouch.
- **Labeling:** The labeling indicates the *Drug Release Test* with which the product complies.
- **USP Reference Standards** ⟨11⟩

USP Nicotine Bitartrate Dihydrate RS

$C_{10}H_{14}N_2 \cdot (C_4H_6O_6)_2 \cdot 2H_2O$ 498.44

USP Nicotine Related Compound D RS

3-(4,5-Dihydro-3*H*-pyrrol-2-yl)pyridine fumarate;
Also known as Myosmine.

$C_9H_{10}N_2 \cdot C_4H_4O_4$ 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.
[Note—This may be a mixture of (1*R*,2*S*) and (1*S*,2*S*) isomers.]

$C_{10}H_{14}N_2O \cdot C_2H_2O_4$ 268.27

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