Status: Currently Official on 16-Feb-2025
Official Date: Official as of 01-Aug-2024
Document Type: USP Monographs
DocId: GUID-C2E26BF6-730F-4AB3-B9BF-CCCCACDE10F9_3_en-US
DOI: https://doi.org/10.31003/USPNF_M8286_03_01
DOI Ref: a4xgi

Rotigotine Transdermal System

DEFINITION

Rotigotine Transdermal System contains NLT 90.0% and NMT 110.0% of the labeled amount of rotigotine ($C_{19}H_{25}NOS$).

IDENTIFICATION

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

Extraction solvent: Prepare a mixture of 2-propanol and *tert*-butylmethylether (80:20). Add 1 mL of methanesulfonic acid to 1 L of the solvent mixture.

Solution A: 0.5 mL of methanesulfonic acid in 1 L of water

Solution B: 0.5 mL of methanesulfonic acid in 1 L of acetonitrile

Mobile phase: *Solution A* and *Solution B* (65:35)

Diluent: 1 mL of methanesulfonic acid in 1 L of water

Standard stock solution: 0.5 mg/mL of USP Rotigotine Hydrochloride RS in *Extraction solvent*. [Note—Sonication in a cooled ultrasonic bath may be used to aid in dissolution.]

Standard solution: Mix 3 mL of the *Standard stock solution* with 7 mL of *Diluent*.

Sample stock solution: Nominally 0.45 mg/mL of rotigotine from NLT 10 Transdermal Systems prepared as follows. Transfer the required number of Transdermal Systems without the release liner to a suitable flask containing *N* mL of *Extraction solvent*, where *N* is the total area of the Transdermal Systems taken. Close the flask and sonicate the solution for NLT 10 min in a sonicator maintained at 20°, shaking the flask intermittently to ensure the silicone matrix is completely dissolved. [Note—Sonication time may be extended if needed to enable complete dissolution of the silicone matrix.]

Sample solution: Mix 3 mL of *Sample stock solution* with 7 mL of *Diluent*. Centrifuge the solution and use the clear supernatant. [Note—A centrifuge speed of NLT 4000 rpm for NLT 15 min may be used.]

Chromatographic system

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

Mode: LC

Detector: UV 272 nm. For *Identification A*, use a diode array detector in the range of 200–400 nm.

Column: 4.0-mm × 7.5-cm; 4-µm packing L7

Column temperature: 30°

Flow rate: 2 mL/min

Injection volume: 10 µL

Run time: NLT 4 times the retention time of rotigotine

System suitability

Sample: *Standard solution*

Suitability requirements

Tailing factor: NMT 2.2

Relative standard deviation: NMT 1.0%

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of rotigotine ($C_{19}H_{25}NOS$) in each Transdermal System taken:

$$\text{Result} = (r_U/r_S) \times C_S \times (V/N) \times (M_{r1}/M_{r2}) \times (1/L) \times 100$$

r_U = peak response from the *Sample solution*

r_S = peak response from the *Standard solution*

C_S = concentration of USP Rotigotine Hydrochloride RS in the *Standard stock solution* (mg/mL)

V = volume of the *Sample stock solution* (mL)

N = number of Transdermal System units used to prepare the *Sample stock solution*

M_{r1} = molecular weight of rotigotine, ▲315.48▲ (CN 1-Aug-2024)

M_{r2} = molecular weight of rotigotine hydrochloride, 351.93

L = label claim (nominal content) of rotigotine in each Transdermal System (mg/unit)

Acceptance criteria: 90.0%–110.0%

PERFORMANCE TESTS

Change to read:

• **Drug Release** ⟨724⟩

Medium: Dissolve 6.9 g of monobasic sodium phosphate in 1 L of water. Adjust with a suitable concentration of sodium hydroxide or phosphoric acid to a pH of 4.5; 900 mL, deaerated.

Apparatus 5: 50 rpm; Transdermal System on metal disk

Times: 15, 30, 60, and 180 min

Solution A, Solution B, and **Mobile phase:** Prepare as directed in the *Assay*.

Standard solution: (*L*/800) mg/mL of USP Rotigotine Hydrochloride RS in *Medium*, where *L* is the label claim in mg/unit

Sample solution: Withdraw 2 mL from the vessel at the specified times.

Chromatographic system

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

Mode: LC

Detector: UV 272 nm

Column: 4.0-mm × 7.5-cm; 4-µm packing L7

Column temperature: 30°

Flow rate: 2 mL/min

Injection volume: 50 µL

Run time: NLT 2.5 times the retention time of rotigotine

System suitability

Sample: *Standard solution*

Suitability requirements

Tailing factor: NMT 2.2 for rotigotine

Relative standard deviation: NMT 2.0% for rotigotine

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount (nominal content) of rotigotine ($C_{19}H_{25}NOS$) released at each time point *i*:

$$\text{Result} = (r_U/r_S) \times C_S \times V \times (1/L) \times (M_{r1}/M_{r2}) \times 100$$

r_U = peak response from the *Sample solution*

r_S = peak response from the *Standard solution*

C_S = concentration of USP Rotigotine Hydrochloride RS in the *Standard solution* (mg/mL)

V = volume of the *Medium*, 900 mL

L = label claim (nominal content) of rotigotine in the Transdermal System (mg/unit)

M_{r1} = molecular weight of rotigotine, ▲315.48▲ (CN 1-Aug-2024)

M_{r2} = molecular weight of rotigotine hydrochloride, 351.93

Acceptance criteria: See *Table 1*.

Table 1

Time Point (*i*)	Time (min)	Rotigotine Released (%)
1	15	14–34
2	30	27–47
3	60	45–65
4	180	NLT 85

The percentages of the labeled amount of rotigotine ($C_{19}H_{25}NOS$) released at the times specified conform to *Drug Release ⟨724⟩, Acceptance Table 1*.

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

IMPURITIES

• **Organic Impurities**

Extraction solvent, Solution A, Solution B, Diluent, and **Standard stock solution:** Prepare as directed in the *Assay*.

Mobile phase: See *Table 2*.

Table 2

Time (min)	Solution A (%)	Solution B (%)
0	95	5
2.0	95	5
35	40	60
38	40	60
39	95	5

Impurities stock solution: 0.1 mg/mL each of USP Rotigotine Related Compound C RS and USP Rotigotine Related Compound K RS in 2-propanol

System suitability stock solution: 0.15 mg/mL of USP Rotigotine Hydrochloride RS and 0.0025 mg/mL each of USP Rotigotine Related Compound C RS and USP Rotigotine Related Compound K RS from suitable volumes of *Standard stock solution* and *Impurities stock solution* in *Extraction solvent*

System suitability solution: Mix 3 mL of *System suitability stock solution* with 7 mL of *Diluent*.

Sensitivity stock solution: 0.25 µg/mL of USP Rotigotine Hydrochloride RS from *Standard stock solution* in *Extraction solvent*

Sensitivity solution: Mix 3 mL of *Sensitivity stock solution* with 7 mL of *Diluent*.

Sample stock solution: [Note—Lacquer removal is recommended to minimize the interferences from the lacquer with the degradation product peaks as follows. Remove the lacquer from the backing foil of each Transdermal System with 4% (v/v) glacial acetic acid in methanol. Dry the lacquer-removed Transdermal Systems for NLT 1 h at room temperature.] Nominally 0.45 mg/mL of rotigotine from NLT 3 Transdermal Systems prepared as follows. Transfer the required number of (lacquer removed, if necessary) Transdermal Systems without the release liner to a suitable flask containing *n* mL of *Extraction solvent*, where *n* is the total area (cm^2) of the Transdermal Systems taken. Close the flask and sonicate the solution for NLT 10 min in a sonicator maintained at 20°, shaking the flask intermittently to ensure the silicone matrix is completely dissolved. [Note—Sonication time may be extended if needed to enable complete dissolution of the silicone matrix.]

Sample solution: Mix 3 mL of *Sample stock solution* with 7 mL of *Diluent*. Centrifuge the solution and use the clear supernatant. [Note—A centrifuge speed of NLT 4000 rpm for NLT 15 min may be used.]

Chromatographic system

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

Mode: LC

Detector: UV 220 nm

Column: 4.6-mm × 12.5-cm; 5-µm packing L10. [NOTE—A guard column with dimensions 4-mm × 1-cm with 5-µm L3 packing is recommended to minimize interference from the adhesive.]

Column temperature: 40°

Flow rate: 1 mL/min

Injection volume: 80 µL

System suitability

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

[NOTE—See *Table 3* for relative retention times.]

Suitability requirements

Resolution: NLT 2.0 between rotigotine related compound K and rotigotine related compound C, *System suitability solution*

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

Analysis

Sample: *Sample solution*

Calculate the percentage of each specified or unspecified degradation product in the portion of the Transdermal System taken:

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

r_U = peak response of each specified or unspecified degradation product from the *Sample solution*

r_T = sum of all the peak responses (including the rotigotine peak) from the *Sample solution*

F = relative response factor (see *Table 3*)

Acceptance criteria: See *Table 3*.

Table 3

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Desthienylethyl rotigotine[a]	0.36	1.0	0.40
Rotigotine related compound K	0.6	3.5	0.20
Rotigotine related compound C	0.7	1.0	0.60
Rotigotine	1.0	—	—
Any individual unspecified degradation product	—	1.0	0.20
Total degradation products	—	—	1.0

[a] (*S*)-6-(Propylamino)-5,6,7,8-tetrahydronaphthalen-1-ol.

ADDITIONAL REQUIREMENTS

• **PACKAGING AND STORAGE:** Preserve in well-closed containers. Store at controlled room temperature.

• **LABELING:** The label states the total amount of rotigotine in the Transdermal System and the release rate, in mg/day, for the duration of the application of one system.

• **USP REFERENCE STANDARDS ⟨11⟩**

USP Rotigotine Hydrochloride RS

(6*S*)-6-[Propyl(2-(2-thienyl)ethyl)amino]-5,6,7,8-tetrahydro-1-naphthalenol hydrochloride.

$C_{19}H_{25}NOS \cdot HCl$ 351.93

USP Rotigotine Related Compound C RS

(*S*)-6-{[2-(Thiophen-2-yl)ethyl]amino}-5,6,7,8-tetrahydronaphthalen-1-ol.

$C_{16}H_{19}NOS$ 273.39

USP Rotigotine Related Compound K RS
7,8-Dihydronaphthalen-1-ol.
$C_{10}H_{10}O$ 146.19

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

Topic/Question	Contact	Expert Committee
ROTIGOTINE TRANSDERMAL SYSTEM	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

Most Recently Appeared In:
Pharmacopeial Forum: Volume No. PF 43(5)

Current DocID: GUID-C2E26BF6-730F-4AB3-B9BF-CCCCACDE10F9_3_en-US
DOI: https://doi.org/10.31003/USPNF_M8286_03_01
DOI ref: a4xgi