Edition: BP 2025 (Ph. Eur. 11.6 update)

Nicotine Sublingual Tablets

General Notices

Action and use

Central nervous system stimulant; nicotine replacement therapy.

DEFINITION

Nicotine Sublingual Tablets contain Nicotine as a *β-cyclodextrin* complex.

The sublingual tablets comply with the requirements stated under Oromucosal Preparations and with the following requirements.

Content of nicotine $C_{10}H_{14}N_2$

95.0 to 105.0% of the stated amount.

Carry out all of the following procedures protected from light.

IDENTIFICATION

Mix a quantity of the powdered tablets containing the equivalent of 20 mg of nicotine with 10 mL of *chloroform*. Disperse with the aid of ultrasound for 30 minutes and centrifuge for 10 minutes. Cool the mixture to 15°, add two 3-mL quantities of 0.5M *hydrochloric acid* and mix carefully. Centrifuge the mixture for 10 minutes. Transfer 5 mL of the aqueous layer to a separating funnel and add sufficient 0.5M *sodium hydroxide* to obtain a pH of 10.5, add 3 mL of *chloroform*, shake and retain the chloroform layer. The *infrared absorption spectrum* of the solution, Appendix II A, is concordant with the *reference spectrum* of nicotine *(RS 452)*.

TESTS

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in 0.2M *potassium dihydrogen orthophosphate* adjusted to pH 2.0 with *orthophosphoric acid* (solvent A).

(1) To a quantity of the powdered tablets containing the equivalent of 20 mg of nicotine add 50 mL of solvent A, mix with the aid of ultrasound and filter through a 0.7-µm glass filter.
(2) Dilute 1 volume of solution (1) to 100 volumes.
(3) Dilute 1 volume of solution (2) to 10 volumes.
(4) 0.124% w/v of *nicotine impurity standard BPCRS*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 4.6 mm) packed with *end-capped polar-embedded octadecylsilyl amorphous organosilica polymer* (3.5 µm) (Waters XBridge is suitable) fitted with a guard column (3 cm × 4.6 mm) packed with the same material.

(b) Use gradient elution and the mobile phase described below.
(c) Use a flow rate of 1.0 mL per minute.
(d) Use an ambient column temperature.
(e) Use a detection wavelength of 254 nm.
(f) Inject 20 µL of each solution.

MOBILE PHASE

Mobile phase A Dilute 25 volumes of 1M *acetic acid* to 1000 volumes with *water*, add 6.2 volumes of 18M *ammonia* and adjust the pH to 10 with 18M *ammonia*.

Mobile phase B *acetonitrile*.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-3	100→95	0→5	linear gradient
3-32	95→60	5→40	linear gradient
32-37	60→100	40→0	linear gradient
37-45	100	0	re-equilibration

In the chromatogram obtained with solution (4):

identify the peaks due to cotinine, myosmine, *cis*-nicotine-1′-oxide and *trans*-nicotine-1′-oxide.

In the chromatogram obtained with solution (1):

identify any peak corresponding to *cis*-nicotine-1′-oxide and multiply the area of this peak by a correction factor of 1.5;

identify any peak corresponding to *trans*-nicotine-1′-oxide and multiply the area of this peak by a correction factor of 1.5.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (4), the *resolution* between cotinine and *trans*-nicotine-1′-oxide is at least 2.0.

LIMITS

In the chromatogram obtained with solution (1):

the area of any peak corresponding to cotinine is not greater than 0.5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.5%);

the area of any peak corresponding to myosmine is not greater than 0.7 times the area of the principal peak in the chromatogram obtained with solution (2) (0.7%);

the area of any peak corresponding to *cis*-nicotine-1′-oxide is not greater than 0.5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.5%);

the area of any peak corresponding to *trans*-nicotine-1′-oxide is not greater than 0.5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.5%);

the area of any other *secondary peak* is not greater than 0.2 times the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);

the sum of the areas of any other *secondary peaks* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (1.0%);

the sum of the areas of all the *secondary peaks* is not greater than five times the area of the principal peak in the chromatogram obtained with solution (2) (5.0%).

Disregard any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (3) (0.1%).

Uniformity of content

Tablets containing less than 2 mg and/or less than 2% w/w of nicotine comply with the requirements stated under Oromucosal Preparations using the following method of analysis. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in 0.2M *potassium dihydrogen orthophosphate* adjusted to pH 2.0 with *orthophosphoric acid* (solvent A).

(1) To one finely-powdered tablet add 50 mL of solvent A, mix with the aid of ultrasound and filter through a 0.7-µm glass filter.
(2) Prepare a suitable solution of *nicotine ditartrate dihydrate BPCRS* in solvent A.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related substances may be used.

DETERMINATION OF CONTENT

Calculate the total content of $C_{10}H_{14}N_2$ in each tablet using the declared content of $C_{10}H_{14}N_2$ in *nicotine ditartrate dihydrate BPCRS*. Each mg of $C_{10}H_{14}N_2$ is equivalent to 3.074 mg of $C_{10}H_{14}N_2,C_8H_{12}O_{12},2H_2O$.

ASSAY

For tablets containing less than 2 mg and/or less than 2% w/w of nicotine.

Use the average of the individual results determined in the test for Uniformity of content.

For tablets containing 2 mg or more and 2% w/w or more of nicotine.

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in 0.2M *potassium dihydrogen orthophosphate* adjusted to pH 2.0 with *orthophosphoric acid* (solvent A).

(1) To a quantity of the powdered tablets containing the equivalent of 20 mg of nicotine add 50 mL of solvent A, mix with the aid of ultrasound and filter through a 0.7-µm glass filter. Dilute 2 mL of the resulting solution to 20 mL with solvent A.
(2) 0.0124% w/v of *nicotine ditartrate dihydrate BPCRS*.
(3) 0.0124% w/v of *nicotine impurity standard BPCRS*.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related substances may be used.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between cotinine and *trans*-nicotine-1′-oxide is at least 2.0.

DETERMINATION OF CONTENT

Calculate the total content of $C_{10}H_{14}N_2$ in each tablet using the declared content of $C_{10}H_{14}N_2$ in *nicotine ditartrate dihydrate BPCRS*. Each mg of $C_{10}H_{14}N_2$ is equivalent to 3.074 mg of $C_{10}H_{14}N_2,C_8H_{12}O_{12},2H_2O$.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Nicotine.