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

Nicotine Resinate Medicated Chewing Gum

General Notices

Action and use

Central nervous system stimulant; nicotine replacement therapy.

DEFINITION

Nicotine Resinate Medicated Chewing Gum contains Nicotine Resinate in a suitable gum basis.

The medicated chewing gum complies with the requirements stated under Medicated Chewing Gums and with the following requirements.

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

90.0 to 113.5% of the stated amount.

Carry out all of the following procedures protected from light.

IDENTIFICATION

Cut a quantity of gum containing the equivalent of 20 mg of nicotine into small pieces, place in a centrifuge tube and add 10 mL of *chloroform*. Place in an ultrasonic bath 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. 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

Dissolution

Carry out the test for *drug release from medicated chewing gum,* Appendix XII B4, using the following conditions.

(1) Use a dissolution medium volume of 20.0 mL prepared from equal volumes of *phosphate buffer solution, pH 7.4* and 0.2% w/v *sodium dodecyl sulfate* at a temperature of 37°, as the medium.
(2) Use a chewing frequency of 60 cycles per minute.
(3) Take samples at 30 minutes.

Insert a whole gum into the chewing chamber and start the chewing process. At the appropriate sampling time withdraw 3 mL of the dissolution medium through a 5-mL syringe. Filter through a 0.4-µm PTFE filter, discard the first 2 mL and use the remaining 1 mL for analysis.

PROCEDURE

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Use the filtered solution from the chewing chamber.
(2) Dissolve a quantity of *nicotine ditartrate dihydrate BPCRS* in the dissolution medium to produce a solution equivalent to the concentration of the final solution expected for solution (1).

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (5 cm × 4.6 mm) packed with *end-capped polar-embedded octadecylsilyl amorphous organosilica polymer* (3.5 µm) (Waters XBridge is suitable).
(b) Use isocratic elution using the mobile phase described below.
(c) Use a flow rate of 1.0 mL per minute.
(d) Use a column temperature of 35°.
(e) Use a detection wavelength of 260 nm.
(f) Inject 20 µL of each solution.

MOBILE PHASE

150 volumes of *acetonitrile*, 425 volumes of 1M *ammonium hydroxide* and 425 volumes of 0.1M *ammonium phosphate*.

DETERMINATION OF CONTENT

Calculate the total content of nicotine, $C_{10}H_{14}N_2$, in the medium using the declared content of $C_{10}H_{14}N_2$ in *nicotine ditartrate dihydrate BPCRS*.

LIMITS

The amount of nicotine, $C_{10}H_{14}N_2$, released is not less than 70% (Q) of the stated amount.

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) Transfer a quantity of gum containing the equivalent of 20 mg of nicotine into a separating funnel, add 50 mL of solvent A, 100 mL of *hexane* and shake for at least 45 minutes or until all of the gum has dissolved. Remove the lower aqueous layer and filter through a 0.4-µm PTFE filter.
(2) Dilute 1 volume of solution (1) to 100 volumes.
(3) Dilute 1 volume of solution (2) to 10 volumes.
(4) 0.04% 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* column (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 using 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 Add 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 in the chromatogram corresponding to *cis*-nicotine-1′-oxide and multiply the area of this peak by a correction factor of 1.5;

identify any peak in the chromatogram 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 *trans*-nicotine-1′-oxide and cotinine 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 0.6 times the area of the principal peak in the chromatogram obtained with solution (2) (0.6%);

the area of any peak corresponding to myosmine is not greater than 0.6 times the area of the principal peak in the chromatogram obtained with solution (2) (0.6%);

the area of any peak corresponding to *cis*-nicotine-1′-oxide is not greater than 3 times the area of the principal peak in the chromatogram obtained with solution (2) (3.0%);

the area of any peak corresponding to *trans*-nicotine-1′-oxide is not greater than 4.5 times the area of the principal peak in the chromatogram obtained with solution (2) (4.5%);

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 *secondary peaks* is not greater than 7.7 times the area of the principal peak in the chromatogram obtained with solution (2) (7.7%).

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

ASSAY

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

(1) Transfer a quantity of gum containing the equivalent of 20 mg of nicotine into a 500 mL separating flask, add 50 mL of solvent A and 100 mL of *hexane* and shake for at least 45 minutes or until all of the gum has dissolved. Remove the lower aqueous layer and filter through a 0.4-µm filter. Dilute 1 volume of the resulting solution to 10 volumes.
(2) 0.0124% w/v of *nicotine ditartrate dihydrate BPCRS*.
(3) 0.04% 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 *trans*-nicotine-1′-oxide and cotinine at least 2.0.

DETERMINATION OF CONTENT

Calculate the total content of nicotine, $C_{10}H_{14}N_2$, in the gum using the declared content of $C_{10}H_{14}N_2$ in *nicotine ditartrate dihydrate BPCRS*.

IMPURITIES

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