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

Donepezil Oral Solution

General Notices

Action and use

Acetylcholinesterase inhibitor; treatment of dementia in Alzheimer's disease.

DEFINITION

Donepezil Oral Solution contains Donepezil Hydrochloride in a suitable flavoured vehicle.

The oral solution complies with the requirements stated under Oral Liquids and with the following requirements.

Content of donepezil hydrochloride, $C_{24}H_{29}NO_3,HCl$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

In the Assay, record the UV spectrum of the principal peak in the chromatograms obtained with solutions (1) and (2) with a diode array detector in the range of 210 to 400 nm.

The UV spectrum of the principal peak in the chromatogram obtained with solution (1) is concordant with that of the peak in the chromatogram obtained with solution (2);

the retention time of the principal peak in the chromatogram obtained with solution (1) is similar to that of the peak in the chromatogram obtained with solution (2).

TESTS

Related substances

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

Solution A 1 volume of 0.1M *hydrochloric acid* and 3 volumes of *methanol*.

(1) Dilute a volume of the oral solution containing 4 mg of Donepezil Hydrochloride to 10 mL and filter (a 0.45-µm PVDF filter is suitable).
(2) Dilute 1 volume of solution (1) to 200 volumes.
(3) 0.02% w/v of *donepezil impurity standard BPCRS*.
(4) Dilute 1 volume of solution (2) to 5 volumes.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 4.6 mm) packed with *end-capped extra-dense bonded octadecylsilyl silica gel for chromatography* (5 µm) (Zorbax Eclipse XDB C18 is suitable).
(b) Use gradient elution and the mobile phase described below.

(c) Use a flow rate of 1.4 mL per minute.
(d) Use a column temperature of 35°.
(e) Use a detection wavelength of 271 nm.
(f) Inject 20 µL of each solution.

MOBILE PHASE

Mobile phase A 1 volume of *perchloric acid*, 350 volumes of *acetonitrile* and 650 volumes of a 0.385% w/v solution of *sodium decanesulfonate* in *water*. Adjust the mixture to pH 1.8 with *perchloric acid*.

Mobile phase B *acetonitrile*.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-13	100	0	isocratic
13-20	100→30	0→70	linear gradient
20-21	30→100	70→0	linear gradient
21-28	100	0	re-equilibration

SYSTEM SUITABILITY

The test is not valid unless:

in the chromatogram obtained with solution (3), the *resolution* between the peaks due to donepezil and impurity 1 is at least 2.0;

in the chromatogram obtained with solution (4), the *signal-to-noise ratio* for the peak due to donepezil is at least 20.

CALCULATION OF IMPURITIES

For each impurity, use the concentration of donepezil hydrochloride in solution (2).

For the reporting threshold, use the concentration of donepezil hydrochloride in solution (4).

For peak identification, use solution (3).

Donepezil retention time: about 12 minutes.

Relative retention: impurity A, about 0.3; impurity 2, about 0.6; impurity F, about 0.9; impurity 1, about 1.2 and impurity 3, about 1.7.

Correction factor: impurity 2, multiply by 1.6.

LIMITS

— unspecified impurities: for each impurity, not more than 0.2%;

— total impurities: not more than 0.4%;

— reporting threshold: 0.1%.

ASSAY

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

(1) Dilute a volume of the oral solution to produce a solution containing 0.0025% w/v of Donepezil Hydrochloride and filter (a 0.45-µm nylon filter is suitable).
(2) 0.0025 % w/v of *donepezil hydrochloride BPCRS*.
(3) 0.0025% w/v of *donepezil impurity standard BPCRS*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (5 µm) (Gemini C18 is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 1.5 mL per minute.
(d) Use a column temperature of 30°.
(e) Use a detection wavelength of 230 nm.
(f) Inject 20 µL of each solution.

MOBILE PHASE

40 volumes of *methanol* and 60 volumes of 0.1M *potassium dihydrogen orthophosphate* adjusted to pH 5.0 with *triethylamine*.

When the chromatograms are recorded under the prescribed conditions the retention time of donepezil is about 8 minutes.

SYSTEM SUITABILITY

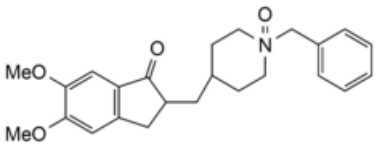
The Assay is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to donepezil and impurity 1 is at least 6.0.

DETERMINATION OF CONTENT

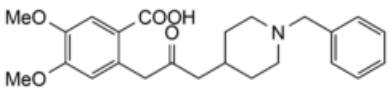
Calculate the content of $C_{24}H_{29}NO_3$,HCl from the chromatograms obtained and using the declared content of $C_{24}H_{29}NO_3$,HCl in *donepezil hydrochloride BPCRS*.

IMPURITIES

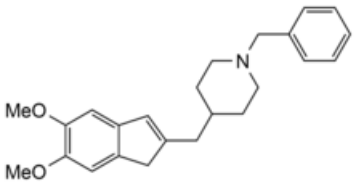
The impurities limited by the requirements of this monograph include impurities A, C and F listed under Donepezil Hydrochloride and:



1. 2-[(1-benzylpiperidin-4-yl)methyl]-5,6-dimethoxyindan-1-one *N*-oxide (donepezil *N*-oxide)



2. 2-(3-(1-benzylpiperidin-4-yl)-2-oxopropyl)-4,5-dimethoxybenzoic acid



3. 1-benzyl-4-(5,6-dimethoxy-1*H*-2-indenyl-methyl) piperidine.