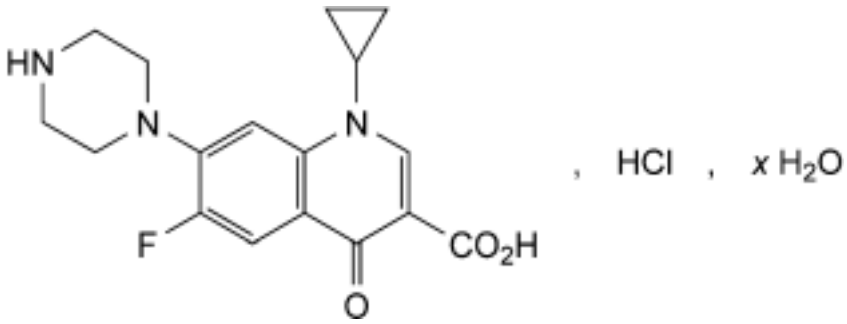
Ciprofloxacin hydrochloride (Ciprofloxacini hydrochloridum)

2020-01

Graphic formula



Molecular formula. $C_{17}H_{18}FN_3O_3$,HCl,xH_2O

Relative molecular mass. 367.8 (anhydrous), 385.8 (monohydrate), 394.8 (sesquihydrate)

Chemical name. 1-Cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinolinecarboxylic acid hydrochloride; CAS Reg. No. 86483-48-9 (anhydrous), 86393-32-0 (monohydrate).

Description. A pale yellow, crystalline powder.

Solubility. Soluble in water R, slightly soluble in methanol R, very slightly soluble in dehydrated ethanol R, practically insoluble in acetone R, in ethyl acetate R and in dichloromethane R.

Category. Antibacterial, antituberculosis.

Storage. Ciprofloxacin hydrochloride should be kept in a tightly closed container, protected from light.

Additional information. Ciprofloxacin hydrochloride is slightly hygroscopic and contains a variable quantity of water.

Requirements

Definition. Ciprofloxacin hydrochloride contains not less than 98.0% and not more than 102.0% ("Assay", Method A) and not less than 99.0% and not more than 101.0% ("Assay", Method B) of ciprofloxacin hydrochloride ($C_{17}H_{18}FN_3O_3$,HCl) calculated with reference to the anhydrous substance.

Identity tests

-Either tests A and D or tests B, C and D may be applied.

Carry out the examination as described under 1.7 Spectrophotometry in the infrared region. The infrared absorption spectrum is concordant with the spectrum obtained from ciprofloxacin hydrochloride RS or with the *reference spectrum* of ciprofloxacin hydrochloride.

Carry out the test as described under *1.14.1 Chromatography*, Thin-layer chromatography, using silica gel R6 as the coating substance and a mixture of 1 volume of acetonitrile R, 2 volumes of ammonia (~260 g/L) TS, 4 volumes of methanol R, and 4 volumes of dichloromethane R as the mobile phase. Apply separately to the plate as 1 cm bands, 5 µL of each of the following 2 solutions containing: (A) 10 mg of the test substance per mL and (B) 10 mg of ciprofloxacin hydrochloride RS per mL. Place an evaporating-dish containing 50 mL of ammonia (~260 g/l) TS in the chromatographic chamber. Expose the plate to the ammonia vapour in the closed chamber for 15 minutes. Withdraw the plate and transfer to another chromatographic chamber containing the mobile phase to develop. After removing the plate from the chromatographic chamber, allow it to dry in air for about 15 minutes, and examine the chromatogram in ultraviolet light at 254 nm and 366 nm.

The principal spot obtained with solution (A) corresponds in position, appearance and intensity to that obtained with solution (B).

Carry out the test as described under *1.14.1 Chromatography*, High-performance liquid chromatography using the conditions given under test for "Related substances". Prepare the following solutions in a mixture of 87 volumes of buffer solution and 13 volumes of acetonitrile R. For solution (1), dissolve 10.0 mg of the test substance in 100.0 mL. For solution (2), dissolve 10.0 mg of ciprofloxacin hydrochloride RS in 100.0 mL. Inject 20 µL of solution (1) and (2). The retention time of the principal peak in the chromatogram obtained with solution (1) corresponds to the retention time of the peak due to ciprofloxacin in the chromatogram obtained with solution (2).

A 0.1 g/mL solution yields reaction B described under 2.1 General identification tests as characteristic of chlorides.

pH value (*1.13*). pH of a 25 mg/mL solution of the test substance in carbon-dioxide-free water R, 3.5-4.5.

Clarity and colour of solution. A solution, containing 12.5 mg/mL of the test substance in carbon-dioxide-free water R, is clear and not more intensely coloured than reference solution GY5, when compared as described under 1.11.2 Degree of coloration of liquids, *Method II*.

Heavy metals. For the preparation of the test solution dissolve 0.25 g in water R and dilute to 30 mL with the same solvent. Carry out a prefiltration. Determine the heavy metals content in the filtrate as described under 2.3 Limit test for heavy metals, *Procedure 1, Method B*; not more than 20 µg/g.

Sulfated ash (*2.3*). Not more than 1.0 mg/g.

Water. Determine as described under 2.8 Determination of water by Karl Fischer Method, Method A. Use 0.200 g of the test substance. The water content is not more than 67.0 mg/g.

Related substances. Prepare fresh solutions protected from light and perform the test without delay.

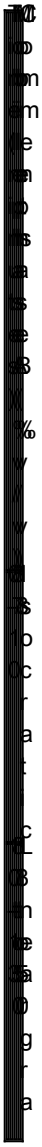
Carry out the test as described under *1.14.1 Chromatography*, High-performance liquid chromatography using a stainless steel column (25 cm x 4.6 mm), packed with end-capped and base-deactivated particles of silica gel, the surface of which has been modified with chemically-bonded octadecylsilyl groups (5 µm).

Prepare the following buffer solution: Carefully add 3.4 mL of phosphoric acid (~1440 g/L) TS to 1600 mL of water R and mix. Adjust the pH with triethylamine R to a pH of 3.0 (+/- 0.1) and dilute to 2000 mL with water R.

Use the following conditions for gradient elution:

mobile phase A: buffer solution

mobile phase B: acetonitrile R.



Operate with a flow rate of 1.5 mL per minute. As a detector, use an ultraviolet spectrophotometer set at a wavelength of 278 nm and, for impurity A, at 263 nm. Maintain the column temperature at 40 °C.

Prepare the solutions (1) to (3) in a mixture of 87 volumes of buffer solution and 13 volumes of acetonitrile R. For solution (1), dissolve 25.0 mg of the test substance in 50.0 mL. For solution (2), dilute 1.0 mL of solution (1) to 100.0 mL. Dilute 1.0 mL of this solution to 10.0 mL. For solution (3), dissolve 2.5 mg of ciprofloxacin hydrochloride for peak identification RS (containing ciprofloxacin and the impurities B, C, D and E) and dilute to 5.0 mL. For solution (4), dissolve 5.0 mg of ciprofloxacin impurity A

RS in 5 mL ammonia (~17 g/L) TS and dilute to 50.0 mL with water R. Dilute 2.0 mL to 100.0 mL with water R.

Inject alternately 30 µL each of solution (1), (2), (3) and (4).

Use the chromatogram obtained with solution (3) to identify the peaks due to the impurities B, C, D and E. Use the chromatogram obtained with solution (4) to identify the peak due to the impurity A. The impurities are eluted at the following relative retention with reference to ciprofloxacin (retention time about 9 minutes); impurity E about 0.4; impurity B about 0.6; impurity C about 0.7; impurity D about 1.2; impurity A about 1.89.

The test is not valid unless, in the chromatogram obtained with solution (3), the resolution between the peaks due to impurity B and the peak due to impurity C is at least 2.0. Also, in the chromatogram obtained with solution (2) the signal-to-noise ratio of the peak due to ciprofloxacin is at least 20 and in the chromatogram obtained with solution (4) the signal-to-noise ratio of the peak due to impurity A is at least 10.

In the chromatogram obtained with solution (1):

- -the area of any peak corresponding to impurity E, when multiplied by a correction factor of 6.7, is not greater than three times the area of the peak due to ciprofloxacin in the chromatogram obtained with solution (2) (0.3 %);
- -the area of any peak corresponding to impurity B, when multiplied by a correction factor of 0.7, is not greater than two times the area of the peak due to ciprofloxacin in the chromatogram obtained with solution (2) (0.2 %);
- -the area of any peak corresponding to impurity C, when multiplied by a correction factor of 0.6, is not greater than two times the area of the peak due to ciprofloxacin in the chromatogram obtained with solution (2) (0.2 %);
- -the area of any peak corresponding to impurity D, when multiplied by a correction factor of 1.4, is not greater than two times the area of the peak due to ciprofloxacin in the chromatogram obtained with solution (2) (0.2 %);
- -the area of any peak corresponding to impurity A, recorded at 263 nm, is not greater than two times the area of the peak due to impurity A, recorded at 263 nm, in the chromatogram obtained with solution (4) (0.2%);
- -the area of any other impurity peak is not greater than the area of the peak due to ciprofloxacin in the chromatogram obtained with solution (2) (0.10 %).
- -The sum of the all other impurity peaks, other than any peak corresponding to impurity A, including the corrected areas of any peaks corresponding to impurity E , B, C or D, is not greater than five times the area of the peak due to ciprofloxacin in the chromatogram obtained with solution (2) (0.5 %). Disregard any peak with an area less than 0.5 times the area of the peak due to ciprofloxacin in the chromatogram in the chromatogram obtained with solution (2) (0.05%).

Assay

-Either test A or test B may be applied.

Carry out the test as described under *1.14.1 Chromatography*, High-performance liquid chromatography, using the conditions given under "Related substances" with the following modifications.

Prepare the following solutions in a mixture of 87 volumes of buffer solution and 13 volumes of acetonitrile R. For solution (1), dissolve 50.0 mg of the test substance in 100.0 mL. For solution (2), dissolve 50.0 mg of Ciprofloxacin hydrochloride RS in 100.0 mL.

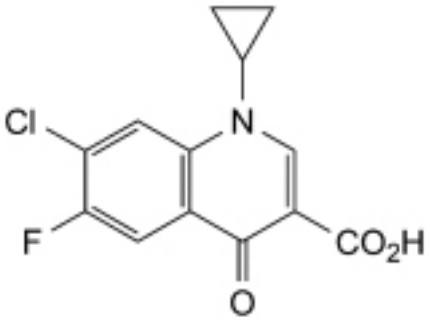
Inject alternately 10 µL each of solution (1) and (2).

Measure the areas of the peaks corresponding to ciprofloxacin obtained in the chromatograms of solution (1) and (2) and calculate the percentage content of ciprofloxacin hydrochloride ($C_{17}H_{18}FN_3O_3$,HCl) using the declared content of $C_{17}H_{18}FN_3O_3$,HCl in ciprofloxacin hydrochloride RS .

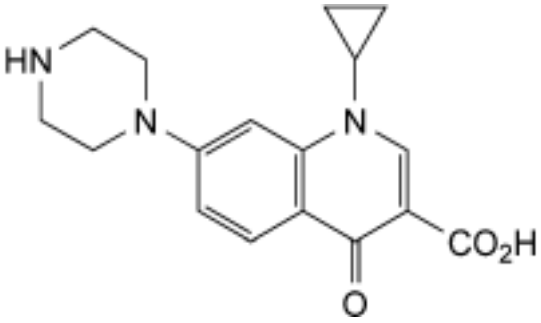
Prepare fresh solutions protected from light and perform the test without delay.

Dissolve 0.300 g in 80 mL of glacial acetic acid R and titrate with perchloric acid (0.1 mol/L) VS as described under *2.6. Non-aqueous titrations*, determining the end point potentiometrically. Each mL of perchloric acid (0.1 mol/L) VS is equivalent to 36.78 mg of $C_{17}H_{18}FN_3O_3$,HCl.

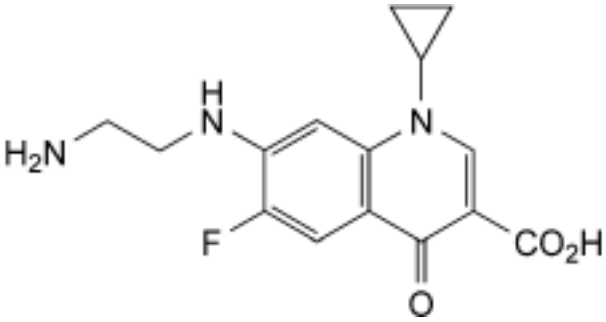
Impurities



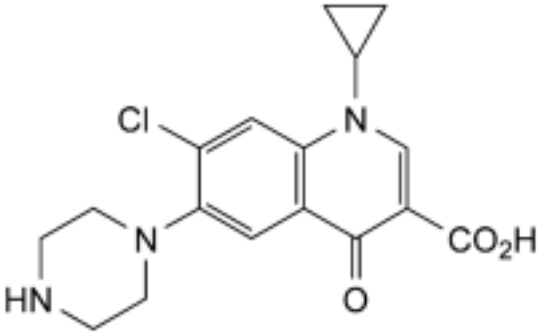
A. 7-chloro-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (fluoroquinolonic acid) (synthesis related impurity)



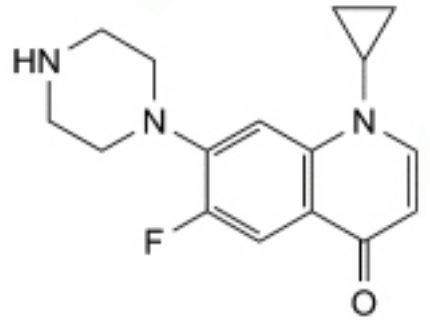
B. 1-cyclopropyl-4-oxo-7-(piperazin-1-yl)-1,4-dihydroquinoline-3-carboxylic acid (desfluoro compound) (synthesis related impurity)



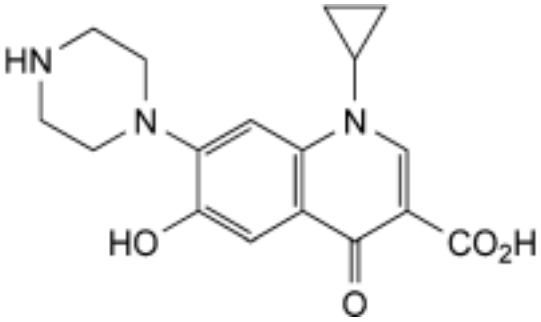
C. 7-[(2-aminoethyl)amino]-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (ethylenediamine compound) (degradation product)



D. 7-chloro-1-cyclopropyl-4-oxo-6-(piperazin-1-yl)-1,4-dihydroquinoline-3-carboxylic acid (7-Chloro-6-piperazinyl analog) (synthesis related impurity)



E. 1-cyclopropyl-6-fluoro-7-(piperazin-1-yl)quinolin-4(1*H*)-one (decarboxylated compound) (degradation product, synthesis related impurity)



F. 1-cyclopropyl-6-hydroxy-4-oxo-7-(piperazin-1-yl)-1,4-dihydroquinoline-3-carboxylic acid (synthesis related impurity)