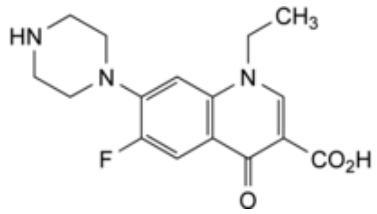
Edition: BP 2025 (Ph. Eur. 11.6 update)

Norfloxacin

General Notices

(Ph. Eur. monograph 1248)



$C_{16}H_{18}FN_3O_3$ 319.3 *70458-96-7*

Action and use

Fluoroquinolone antibacterial.

Preparation

Norfloxacin Tablets

Ph Eur

DEFINITION

1-Ethyl-6-fluoro-4-oxo-7-(piperazin-1-yl)-1,4-dihydroquinoline-3-carboxylic acid.

Content

99.0 per cent to 101.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White or pale yellow, hygroscopic, photosensitive, crystalline powder.

Solubility

Very slightly soluble in water, slightly soluble in acetone and in ethanol (96 per cent).

It shows polymorphism (5.9).

IDENTIFICATION

Infrared absorption spectrophotometry (2.2.24).

Comparison norfloxacin CRS.

If the spectra obtained in the solid state show differences, dissolve the substance to be examined and the reference substance separately in methylene chloride R, evaporate to dryness in a water-bath at 45 °C, dry in an oven at 105 °C for about 1 h and record new spectra using the residues.

TESTS

Appearance of solution

Dissolve 0.5 g in a previously filtered 4 g/L solution of sodium hydroxide R in methanol R and dilute to 50 mL with the same solution. The solution is not more opalescent than reference suspension II (2.2.1) and not more intensely coloured than reference solution B_7 (2.2.2, Method II).

Related substances

Liquid chromatography (2.2.29).

Solvent mixture acetonitrile R, water R adjusted to pH 2.0 with phosphoric acid R (5:95 *V/V*).

Test solution Dissolve 20.0 mg of the substance to be examined in 25 mL of the solvent mixture using sonication, and dilute to 50.0 mL with the solvent mixture.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with the solvent mixture. Dilute 1.0 mL of this solution to 10.0 mL with the solvent mixture.

Reference solution (b) Dissolve 4 mg of norfloxacin for system suitability CRS (containing impurities A, E and H) in 5 mL of the solvent mixture using sonication, and dilute to 10 mL with the solvent mixture.

Reference solution (c) Dissolve 4 mg of norfloxacin for peak identification CRS (containing impurity K) in 5 mL of the solvent mixture using sonication, and dilute to 10 mL with the solvent mixture.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: end-capped amidohexadecylsilyl silica gel for chromatography R (5 µm);

— *temperature*: 60 °C.

Mobile phase:

— *mobile phase A*: water for chromatography R adjusted to pH 2.0 with phosphoric acid R;

— *mobile phase B*: acetonitrile R;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 5	95	5
5 - 7	95 → 93	5 → 7
7 - 10	93 → 87	7 → 13
10 - 15	87 → 47	13 → 53
15 - 20	47 → 10	53 → 90

Flow rate 1.4 mL/min.

Detection Spectrophotometer at 265 nm.

Injection 20 µL.

Identification of impurities Use the chromatogram supplied with *norfloxacin for system suitability CRS* and the chromatogram obtained with reference solution (b) to identify the peaks due to impurities A, E and H; use the chromatogram supplied with *norfloxacin for peak identification CRS* and the chromatogram obtained with reference solution (c) to identify the peak due to impurity K.

Relative retention With reference to norfloxacin (retention time = about 11 min): impurity K = about 0.6; impurity E = about 0.97; impurity A = about 1.5; impurity H = about 1.6.

System suitability Reference solution (b):

— *resolution*: minimum 3.0 between the peaks due to impurities A and H;

— *peak-to-valley ratio*: minimum 5.0, where H_p = height above the baseline of the peak due to impurity E and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to norfloxacin.

Limits:

— *impurities E, K*: for each impurity, not more than 1.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.15 per cent);

— *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.10 per cent);

— *total*: not more than 5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.5 per cent);

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

Water (*2.5.12*)

Maximum 1.0 per cent, determined on 0.700 g. Use as the solvent a mixture of 10 mL of *anhydrous methanol R* and 20 mL of *formamide R*.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g in a platinum crucible.

ASSAY

Dissolve 0.240 g in 80 mL of *anhydrous acetic acid R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (*2.2.20*).

1 mL of *0.1 M perchloric acid* is equivalent to 31.93 mg of $C_{16}H_{18}FN_3O_3$.

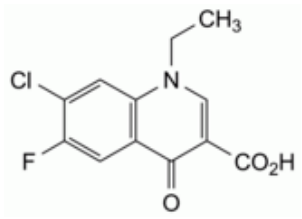
STORAGE

In an airtight container, protected from light.

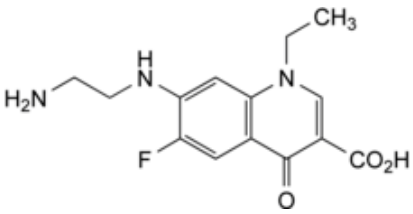
IMPURITIES

Specified impurities E, K.

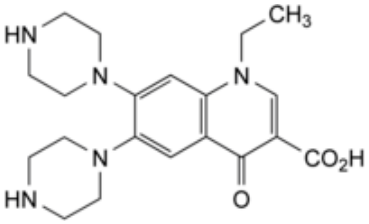
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) A, B, C, D, F, G, H, I, J.



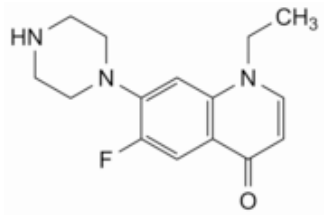
A. 7-chloro-1-ethyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid,



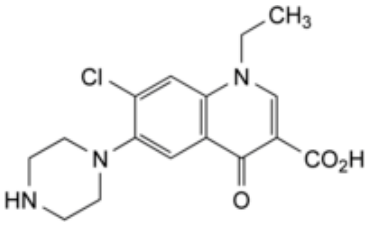
B. 7-[(2-aminoethyl)amino]-1-ethyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid,



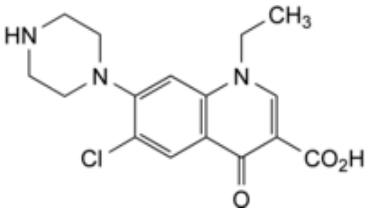
C. 1-ethyl-4-oxo-6,7-di(piperazin-1-yl)-1,4-dihydroquinoline-3-carboxylic acid,



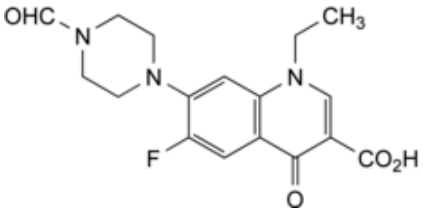
D. 1-ethyl-6-fluoro-7-(piperazin-1-yl)quinolin-4(1*H*)-one,



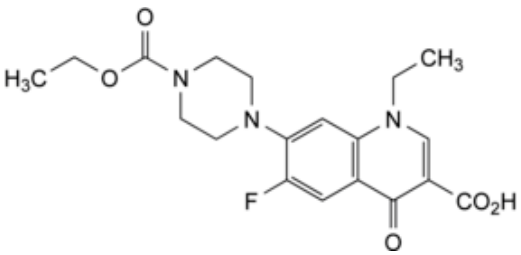
E. 7-chloro-1-ethyl-4-oxo-6-(piperazin-1-yl)-1,4-dihydroquinoline-3-carboxylic acid,



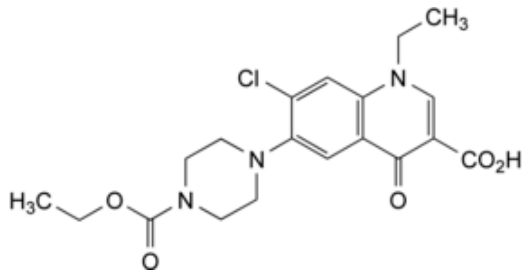
F. 6-chloro-1-ethyl-4-oxo-7-(piperazin-1-yl)-1,4-dihydroquinoline-3-carboxylic acid,



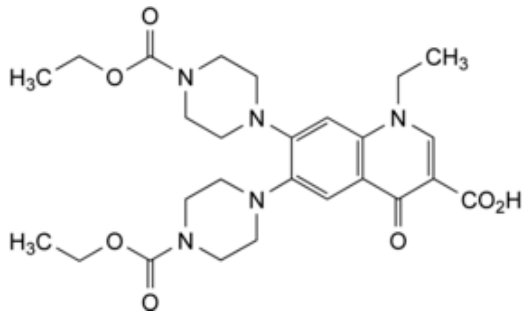
G. 1-ethyl-6-fluoro-7-(4-formylpiperazin-1-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid,



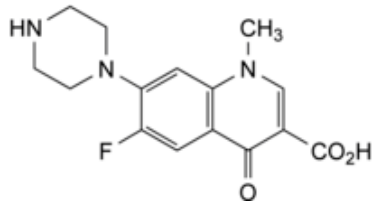
H. 7-[4-(ethoxycarbonyl)piperazin-1-yl]-1-ethyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid,



I. 7-chloro-6-[4-(ethoxycarbonyl)piperazin-1-yl]-1-ethyl-4-oxo-1,4-dihydroquinoline-3-carboxylic acid,



J. 6,7-bis[4-(ethoxycarbonyl)piperazin-1-yl]-1-ethyl-4-oxo-1,4-dihydroquinoline-3-carboxylic acid,



K. 6-fluoro-1-methyl-4-oxo-7-(piperazin-1-yl)-1,4-dihydroquinoline-3-carboxylic acid.

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