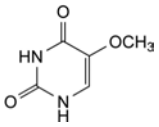
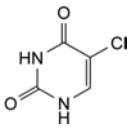
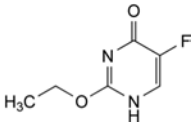


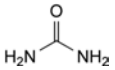
D. 5-methoxypyrimidine-2,4(1*H*,3*H*)-dione (5-methoxyuracil),



E. 5-chloropyrimidine-2,4(1*H*,3*H*)-dione (5-chlorouracil),



F. 2-ethoxy-5-fluoropyrimidin-4(1*H*)-one (2-ethoxy-5-fluorouracil),

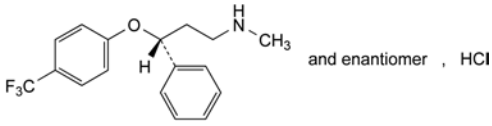


G. carbamide (urea).

01/2011:1104

FLUOXETINE HYDROCHLORIDE

Fluoxetini hydrochloridum



$C_{17}H_{19}ClF_3NO$ M_r 345.8
[56296-78-7]

DEFINITION

(3*RS*)-*N*-Methyl-3-phenyl-3-[4-(trifluoromethyl)phenoxy]-propan-1-amine hydrochloride.

Content: 98.0 per cent to 102.0 per cent (anhydrous substance).

CHARACTERS

Appearance: white or almost white, crystalline powder.

Solubility: sparingly soluble in water, freely soluble in methanol, sparingly soluble in methylene chloride.

IDENTIFICATION

A. Infrared absorption spectrophotometry (*2.2.24*).

Comparison: *fluoxetine hydrochloride CRS*.

B. It gives reaction (a) of chlorides (*2.3.1*).

TESTS

Solution S. Dissolve 2.0 g in a mixture of 15 volumes of *water R* and 85 volumes of *methanol R*, then dilute to 100.0 mL with the same mixture of solvents.

Appearance of solution. Solution S is clear (*2.2.1*) and colourless (*2.2.2, Method II*).

pH (*2.2.3*): 4.5 to 6.5.

Dissolve 0.20 g in *carbon dioxide-free water R* and dilute to 20 mL with the same solvent.

Optical rotation (*2.2.7*): – 0.05° to + 0.05°, determined on solution S.

Related substances. Liquid chromatography (*2.2.29*).

Test solution (a). Dissolve 55 mg of the substance to be examined in the mobile phase and dilute to 10.0 mL with the mobile phase.

Test solution (b). Dilute 2.0 mL of test solution (a) to 10.0 mL with the mobile phase.

Reference solution. Dissolve 22 mg of *fluoxetine hydrochloride CRS* in 10.0 mL of *0.5 M sulfuric acid*. Heat at about 85 °C for 3 h. Allow to cool. The resulting solution contains considerable quantities of impurity A and usually also contains 4-trifluoromethylphenol. To 0.4 mL of this solution add 28.0 mg of *fluoxetine hydrochloride CRS*, about 1 mg of *fluoxetine impurity B CRS* and about 1 mg of *fluoxetine impurity C CRS*, then dilute to 25.0 mL with the mobile phase.

Column:

– *size*: *l* = 0.25 m, Ø = 4.6 mm;
– *stationary phase*: *octylsilyl silica gel for chromatography R* (5 µm).

Mobile phase: mix 8 volumes of *methanol R*, 30 volumes of *tetrahydrofuran R* and 62 volumes of a solution of *triethylamine R* prepared as follows: to 10 mL of *triethylamine R*, add 980 mL of *water R*, mix and adjust to pH 6.0 with *phosphoric acid R* (about 4.5 mL) and dilute to 1000 mL with *water R*.

Flow rate: 1 mL/min.

Detection: spectrophotometer at 215 nm.

Injection: 10 µL.

Run time: 3 times the retention time of fluoxetine.

Identification of impurities: use the chromatogram obtained with the reference solution to identify the peaks due to impurities A, B and C.

Relative retention with reference to fluoxetine: impurity A = about 0.24; impurity B = about 0.27; impurity C = about 0.9.

System suitability: reference solution:

– *retention time*: fluoxetine = 10 min to 18 min; 4-trifluoromethylphenol: maximum 35 min; if no peak due to 4-trifluoromethylphenol is observed, inject a 0.02 per cent solution of *4-trifluoromethylphenol R* in the mobile phase;
– *peak-to-valley ratio*: minimum 11, where H_p = height above the baseline of the peak due to impurity C and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to fluoxetine. If necessary, reduce the volume of methanol and increase the volume of the solution of triethylamine in the mobile phase.

Limit: test solution (b):

– *impurity C*: not more than 0.0015 times the area of the principal peak (0.15 per cent).

Limits: test solution (a):

– *impurities A, B*: for each impurity, not more than 0.0125 times the area of the principal peak in the chromatogram obtained with test solution (b) (0.25 per cent);
– *unspecified impurities*: for each impurity, not more than 0.005 times the area of the principal peak in the chromatogram obtained with test solution (b) (0.10 per cent);
– *total*: not more than 0.025 times the area of the principal peak in the chromatogram obtained with test solution (b) (0.5 per cent);
– *disregard limit*: 0.0025 times the area of the principal peak in the chromatogram obtained with test solution (b) (0.05 per cent).

Acetonitrile. Gas chromatography (*2.2.28*).

Test solution. Dissolve 50 mg of the substance to be examined in *dimethylformamide R* and dilute to 5.0 mL with the same solvent.

Reference solution. To 1.0 g of *acetonitrile R*, add *dimethylformamide R*, mix and dilute to 100.0 mL with the same solvent. Dilute 1.0 mL of this solution to 1000.0 mL with *dimethylformamide R*.

Column:
– *material*: fused silica;
– *size*: *l* = 30 m, Ø = 0.53 mm;
– *stationary phase*: *macrogol 20 000 R* (film thickness 1 µm).
Carrier gas: *helium for chromatography R*.
Flow rate: 10 mL/min.
Temperature:

	Time (min)	Temperature (°C)
Column	0 - 2	35
	2 - 14.33	35 → 220
	14.33 - 24.33	220
Injection port		250
Detector		250

Detection: flame ionisation.
Injection: 1 µL; inject *dimethylformamide R* as a blank.
In the chromatogram obtained with *dimethylformamide R*, verify that there is no peak with the same retention time as acetonitrile.
Limit:
– *acetonitrile*: not more than the area of the corresponding peak in the chromatogram obtained with the reference solution (0.1 per cent).

Heavy metals (*2.4.8*): maximum 20 ppm.
1.0 g complies with test C. Prepare the reference solution using 2 mL of *lead standard solution (10 ppm Pb) R*.

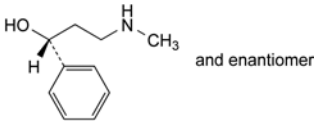
Water (*2.5.12*): maximum 0.5 per cent, determined on 1.00 g.

Sulfated ash (*2.4.14*): maximum 0.1 per cent, determined on 1.0 g.

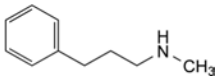
ASSAY

Liquid chromatography (*2.2.29*) as described in the test for related substances with the following modifications.
Test solution. Dissolve 55.0 mg of the substance to be examined in the mobile phase and dilute to 50.0 mL with the mobile phase. Dilute 10.0 mL of this solution to 100.0 mL with the mobile phase.
Reference solution. Dissolve 55.0 mg of *fluoxetine hydrochloride CRS* in the mobile phase and dilute to 50.0 mL with the mobile phase. Dilute 10.0 mL of this solution to 100.0 mL with the mobile phase.
Detection: spectrophotometer at 227 nm.
Retention time: fluoxetine = 10 min to 18 min; if necessary, adjust the volumes of methanol and of the solution of triethylamine in the mobile phase.
System suitability: reference solution:
– *symmetry factor*: maximum 2.0 calculated at 10 per cent of the height of the peak due to fluoxetine.
Calculate the content of $C_{17}H_{19}ClF_3NO$ from the declared content of *fluoxetine hydrochloride CRS*.

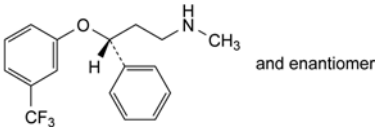
IMPURITIES
Specified impurities: A, B, C.



A. (1*RS*)-3-(methylamino)-1-phenylpropan-1-ol,



B. *N*-methyl-3-phenylpropan-1-amine,

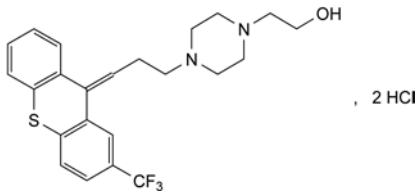


C. (3*RS*)-*N*-methyl-3-phenyl-3-[3-(trifluoromethyl)phenoxy]-propan-1-amine.

01/2008:1693
corrected 6.0

FLUPENTIXOL DIHYDROCHLORIDE

Flupentixoli dihydrochloridum



$C_{23}H_{27}Cl_2F_3N_2OS$ M_r 507.4
[2413-38-9]

DEFINITION

2-[4-[3-[(*EZ*)-2-(trifluoromethyl)-9*H*-thioxanthen-9-ylidene]propyl]piperazin-1-yl]ethanol dihydrochloride.
Content:
– flupentixol dihydrochloride: 98.0 per cent to 101.5 per cent (dried substance),
– *Z*-isomer: 42.0 per cent to 52.0 per cent.

CHARACTERS

Appearance: white or almost white powder.
Solubility: very soluble in water, soluble in alcohol, practically insoluble in methylene chloride.

IDENTIFICATION

First identification: A, D.
Second identification: B, C, D.

A. Infrared absorption spectrophotometry (*2.2.24*).
Comparison: *flupentixol dihydrochloride CRS*.

B. Thin-layer chromatography (*2.2.27*).
Test solution. Dissolve 20 mg of the substance to be examined in *methanol R* and dilute to 10 mL with the same solvent.
Reference solution. Dissolve 20 mg of *flupentixol dihydrochloride CRS* in *methanol R* and dilute to 10 mL with the same solvent.
Plate: *TLC silica gel F_{254} plate R*.
Mobile phase: *water R, diethylamine R, methyl ethyl ketone R* (1:4:95 *V/V/V*).
Application: 2 µL.
Development: twice over a path of 15 cm.
Drying: in air.
Detection A: examine in ultraviolet light at 254 nm.
Results A: the principal spot in the chromatogram obtained with the test solution is similar in position and size to the principal spot in the chromatogram obtained with the reference solution. Doubling of the spot may be observed in both chromatograms.
Detection B: spray with *alcoholic solution of sulfuric acid R*; heat at 110 °C for 5 min and allow to cool; examine in ultraviolet light at 365 nm.

Monographs F-H