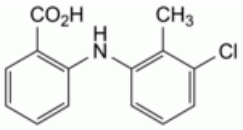
Edition: BP 2025 (Ph. Eur. 11.6 update)

Tolfenamic Acid

General Notices

(Ph. Eur. monograph 2039)



$C_{14}H_{12}ClNO_2$ 261.7 *13710-19-5*

Action and use

Cyclo-oxygenase inhibitor; analgesic; anti-inflammatory.

Ph Eur

DEFINITION

2-(3-Chloro-2-methylanilino)benzoic acid.

Content

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

CHARACTERS

Appearance

White or slightly yellow, crystalline powder.

Solubility

Practically insoluble in water, soluble in dimethylformamide, sparingly soluble in anhydrous ethanol and in methylene chloride. It dissolves in dilute solutions of alkali hydroxides.

mp

About 213 °C.

IDENTIFICATION

First identification: B.

Second identification: A, C.

A. Dissolve 20 mg in a mixture of 1 volume of *1 M hydrochloric acid* and 99 volumes of *methanol R* and dilute to 100 mL with the same mixture of solvents. Dilute 5.0 mL of the solution to 50 mL with a mixture of 1 volume of *1 M hydrochloric acid* and 99 volumes of *methanol R*. Examined between 250 nm and 380 nm (*2.2.25*), the solution shows 2 absorption maxima, at 286 nm and 345 nm. The ratio of the absorbance measured at the maximum at 286 nm to that measured at the maximum at 345 nm is 1.2 to 1.4.
B. Infrared absorption spectrophotometry (*2.2.24*).

Comparison *tolfenamic acid CRS*.

C. Thin-layer chromatography (*2.2.27*).

Test solution Dissolve 25 mg of the substance to be examined in a mixture of 1 volume of *methanol R* and 3 volumes of *methylene chloride R* and dilute to 10 mL with the same mixture of solvents.

Reference solution Dissolve 25 mg of *tolfenamic acid CRS* in a mixture of 1 volume of *methanol R* and 3 volumes of *methylene chloride R* and dilute to 10 mL with the same mixture of solvents.

Plate *TLC silica gel GF_{254} plate R*.

Mobile phase *glacial acetic acid R*, *dioxan R*, *toluene R* (1:25:90 *V/V/V*).

Application 10 µL.

Development Over 2/3 of the plate.

Drying In a current of warm air.

Detection Ultraviolet light at 254 nm.

Results The principal spot in the chromatogram obtained with the test solution is similar in position, colour and size to the principal spot in the chromatogram obtained with the reference solution.

TESTS

Related substances

Liquid chromatography (*2.2.29*).

Test solution Dissolve 50.0 mg of the substance to be examined in 5 mL of *anhydrous ethanol R* and dilute to 50.0 mL with the mobile phase.

Reference solution (a) Dissolve 25.0 mg of *2-chlorobenzoic acid R* (impurity A) and 25.0 mg of *3-chloro-2-methylaniline R* (impurity B) in 5 mL of *anhydrous ethanol R* and dilute to 50.0 mL with the mobile phase. Dilute 1.0 mL of the solution to 50.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 10.0 mL with the mobile phase.

Reference solution (b) Dilute 1.0 mL of the test solution to 10.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 100.0 mL with the mobile phase.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

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

Mobile phase *glacial acetic acid R*, *water for chromatography R*, *anhydrous ethanol R* (0.2:35:65 *V/V/V*).

Flow rate 0.8 mL/min.

Detection Spectrophotometer at 232 nm.

Injection 20 µL.

Run time 3 times the retention time of tolfenamic acid.

Relative retention With reference to tolfenamic acid (retention time = about 15 min): impurity A = about 0.25; impurity B = about 0.34.

System suitability Reference solution (a):

— *resolution*: minimum 2.5 between the peaks due to impurity A and to impurity B.

Limits:

— *impurity A*: not more than the area of the corresponding peak in the chromatogram obtained with reference solution (a) (0.1 per cent);

— *impurity B*: not more than half the area of the corresponding peak in the chromatogram obtained with reference solution (a) (0.05 per cent);

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

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

— *disregard limit*: 0.1 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.01 per cent).

Loss on drying (*2.2.32*)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.200 g with the aid of ultrasound in 100 mL of *anhydrous ethanol R*. Add 0.1 mL of *phenol red solution R* and titrate with *0.1 M sodium hydroxide*.

1 mL of *0.1 M sodium hydroxide* is equivalent to 26.17 mg of $C_{14}H_{12}ClNO_2$.

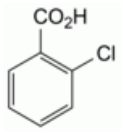
STORAGE

Protected from light.

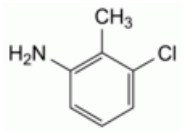
IMPURITIES

Specified impurities *A, B.*

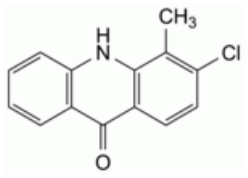
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical 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) *C.*



A. 2-chlorobenzoic acid,



B. 3-chloro-2-methylaniline,



C. 3-chloro-4-methylacridin-9(10*H*)-one.

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