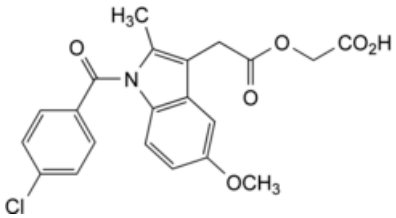
Edition: BP 2025 (Ph. Eur. 11.6 update)

Acemetacin

General Notices

(Ph. Eur. monograph 1686)



$C_{21}H_{18}ClNO_6$ 415.8 *53164-05-9*

Action and use

Cyclo-oxygenase inhibitor; analgesic; anti-inflammatory.

Ph Eur

DEFINITION

[[[1-(4-Chlorobenzoyl)-5-methoxy-2-methyl-1*H*-indol-3-yl]acetyl]oxy]acetic acid.

Content

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

CHARACTERS

Appearance

Yellow or greenish-yellow, crystalline powder.

Solubility

Practically insoluble in water, soluble in acetone, slightly soluble in anhydrous ethanol.

It shows polymorphism (*5.9*).

IDENTIFICATION

Infrared absorption spectrophotometry (*2.2.24*).

Comparison acemetacin CRS.

If the spectra obtained in the solid state show differences, dissolve the substance to be examined and the reference substance separately in acetone R, evaporate to dryness and record new spectra using the residues.

TESTS

Related substances

Liquid chromatography (2.2.29).

Test solution Dissolve 0.100 g of the substance to be examined in acetonitrile for chromatography R and dilute to 20.0 mL with the same solvent.

Reference solution (a) Dilute 5.0 mL of the test solution to 50.0 mL with acetonitrile for chromatography R. Dilute 1.0 mL of this solution to 100.0 mL with acetonitrile for chromatography R.

Reference solution (b) Dissolve 5.0 mg of acemetacin impurity A CRS and 10.0 mg of indometacin CRS (impurity B) in acetonitrile for chromatography R, and dilute to 50.0 mL with the same solvent.

Reference solution (c) Dilute 1.0 mL of reference solution (b) to 20.0 mL with acetonitrile for chromatography R.

Reference solution (d) To 1 mL of reference solution (b), add 10 mL of the test solution and dilute to 20 mL with acetonitrile for chromatography R.

Reference solution (e) Dissolve the contents of a vial of acemetacin impurity mixture CRS (containing impurities C, D, E and F) in 1.0 mL of the test solution.

Column:

— *size*: *l* = 0.25 m, Ø = 4 mm;

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

— *temperature*: 40 °C.

Mobile phase:

— *mobile phase A*: dissolve 1.0 g of potassium dihydrogen phosphate R in 900 mL of water R, adjust to pH 6.5 with 1 M sodium hydroxide and dilute to 1000 mL with water R;

— *mobile phase B*: acetonitrile for chromatography R;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 5	95	5
5 - 9	95 → 65	5 → 35
9 - 16	65	35
16 - 28	65 → 20	35 → 80
28 - 34	20	80

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 235 nm.

Injection 20 µL.

Identification of impurities:

— use the chromatogram supplied with acemetacin impurity mixture CRS and the chromatogram obtained with reference solution (e) to identify the peaks due to impurities C, D, E and F;

— use the chromatogram obtained with reference solution (b) to identify the peak due to impurity B.

Relative retention With reference to acemetacin (retention time = about 15 min): impurity A = about 0.7; impurity B = about 0.9; impurity F = about 1.2; impurity C = about 1.3; impurity D = about 1.5; impurity E = about 2.2.

System suitability Reference solution (d):

— *peak-to-valley ratio*: minimum 15, where H_p = height above the baseline of the peak due to impurity B and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to acemetacin.

Limits:

— *correction factors*: for the calculation of content, multiply the peak areas of the following impurities by the corresponding correction factor: impurity C = 1.3; impurity D = 1.4; impurity F = 1.3;

— *impurity E*: not more than 3 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.3 per cent);

— *impurity B*: not more than the area of the corresponding peak in the chromatogram obtained with reference solution (c) (0.2 per cent);

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

— *impurities C, D, F*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.1 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 4 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.4 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).

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 0.350 g in 20 mL of *acetone R* and add 10 mL of *water R*. Titrate with *0.1 M sodium hydroxide*, determining the end-point potentiometrically (*2.2.20*).

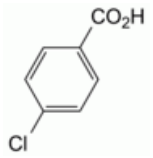
1 mL of *0.1 M sodium hydroxide* is equivalent to 41.58 mg of $C_{21}H_{18}ClNO_6$.

STORAGE

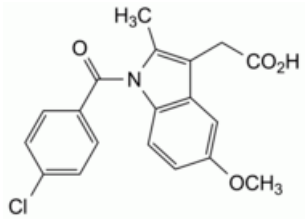
Protected from light.

IMPURITIES

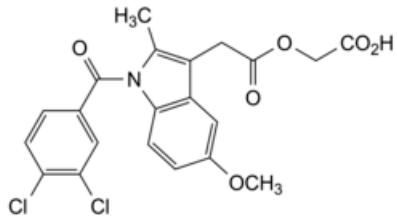
Specified impurities *A, B, C, D, E, F.*



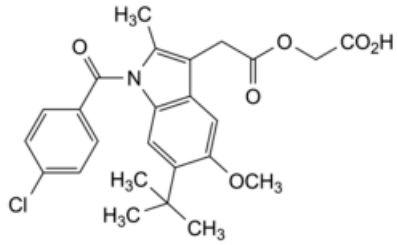
A. 4-chlorobenzoic acid,



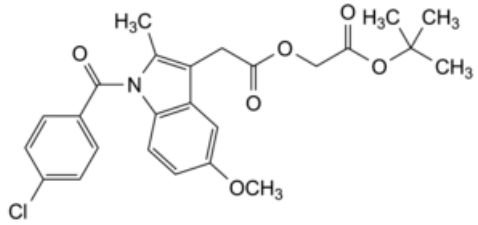
B. [1-(4-chlorobenzoyl)-5-methoxy-2-methylindol-3-yl]acetic acid (indometacin),



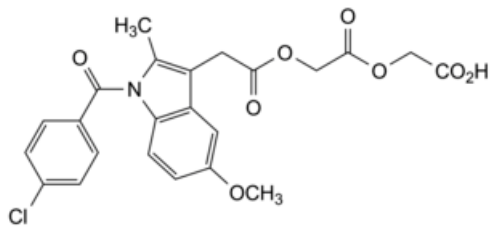
C. [[[1-(3,4-dichlorobenzoyl)-5-methoxy-2-methyl-1*H*-indol-3-yl]acetyl]oxy]acetic acid,



D. [[[1-(4-chlorobenzoyl)-6-(1,1-dimethylethyl)-5-methoxy-2-methyl-1*H*-indol-3-yl]acetyl]oxy]acetic acid,



E. 1,1-dimethylethyl [[[1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1*H*-indol-3-yl]acetyl]oxy]acetate,



F. [[[[[1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1*H*-indol-3-yl]acetyl]oxy]acetyl]oxy]acetic acid.