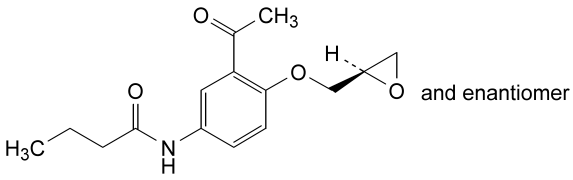
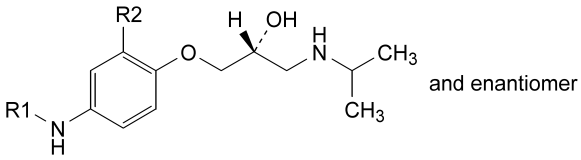
IMPURITIES

Specified impurities: A, B, C, D, E, F, G, H, I, J, K.



A. *N*-[3-acetyl-4-[(2*RS*)-oxiran-2-ylmethoxy]phenyl]butanamide,



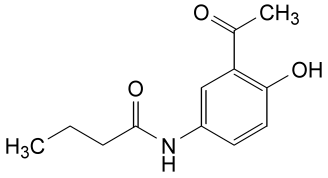
B. R1 = R2 = CO-CH_3: *N*-[3-acetyl-4-[(2*RS*)-2-hydroxy-3-[(1-methylethyl)amino]propoxy]phenyl]acetamide (diacetolol),

D. R1 = H, R2 = CO-CH_3: 1-[5-amino-2-[(2*RS*)-2-hydroxy-3-[(1-methylethyl)amino]propoxy]phenyl]ethanone,

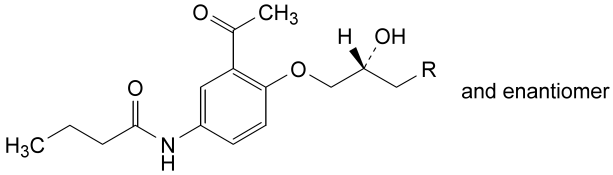
E. R1 = CO-CH_2-CH_2-CH_3, R2 = H: *N*-[4-[(2*RS*)-2-hydroxy-3-[(1-methylethyl)amino]propoxy]phenyl]butanamide,

J. R1 = CO-CH_2-CH_3, R2 = CO-CH_3: *N*-[3-acetyl-4-[(2*RS*)-2-hydroxy-3-[(1-methylethyl)amino]propoxy]phenyl]propanamide,

K. R1 = R2 = CO-CH_2-CH_2-CH_3: *N*-[3-butanoyl-4-[(2*RS*)-2-hydroxy-3-[(1-methylethyl)amino]propoxy]phenyl]butanamide,

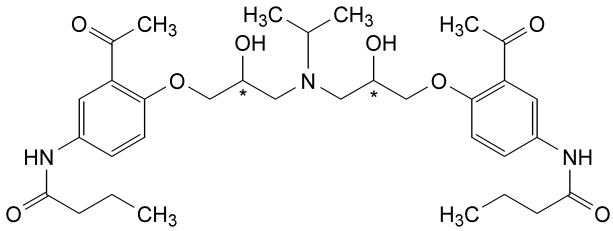


C. *N*-(3-acetyl-4-hydroxyphenyl)butanamide,

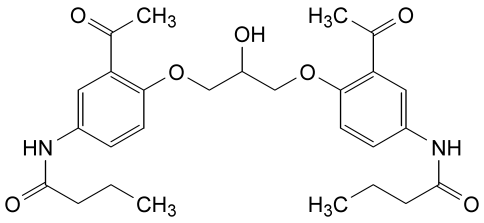


F. R = OH: *N*-[3-acetyl-4-[(2*RS*)-2,3-dihydroxypropoxy]phenyl]butanamide,

I. R = NH-CH_2-CH_3: *N*-[3-acetyl-4-[(2*RS*)-3-(ethylamino)-2-hydroxypropoxy]phenyl]butanamide,



G. *N,N'*-[[(1-methylethyl)imino]bis[(2-hydroxypropane-1,3-diyl)oxy(3-acetyl-1,4-phenylene)]]dibutanamide (biamine),

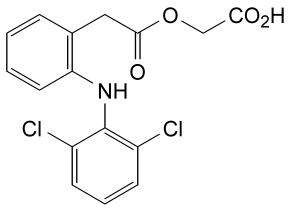


H. *N,N'*-[(2-hydroxypropane-1,3-diyl)bis[oxy(3-acetyl-1,4-phenylene)]]dibutanamide.

01/2008:1281
corrected 6.0

ACECLOFENAC

Aceclofenacum



$C_{16}H_{13}Cl_2NO_4$ M_r 354.2
[89796-99-6]

DEFINITION

[[[2-[(2,6-Dichlorophenyl)amino]phenyl]acetyl]oxy]acetic acid.

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

CHARACTERS

Appearance: white or almost white, crystalline powder.

Solubility: practically insoluble in water, freely soluble in acetone, soluble in alcohol.

IDENTIFICATION

First identification: B.

Second identification: A, C.

A. Dissolve 50.0 mg in *methanol R* and dilute to 100.0 ml with the same solvent. Dilute 2.0 ml of the solution to 50.0 ml with *methanol R*. Examined between 220 nm and 370 nm (*2.2.25*), the solution shows an absorption maximum at 275 nm. The specific absorbance at the absorption maximum is 320 to 350.

B. Infrared absorption spectrophotometry (*2.2.24*).

Comparison: Ph. Eur. reference spectrum of aceclofenac.

C. Dissolve about 10 mg in 10 ml of *alcohol R*. To 1 ml of the solution, add 0.2 ml of a mixture, prepared immediately before use, of equal volumes of a 6 g/l solution of *potassium ferricyanide R* and a 9 g/l solution of *ferric chloride R*. Allow to stand protected from light for 5 min. Add 3 ml of a 10.0 g/l solution of *hydrochloric acid R*. Allow to stand protected from light for 15 min. A blue colour develops and a precipitate is formed.

TESTS

Related substances. Liquid chromatography (*2.2.29*). *Prepare the solutions immediately before use.*

Test solution. Dissolve 50.0 mg of the substance to be examined in a mixture of 30 volumes of mobile phase A and 70 volumes of mobile phase B and dilute to 25.0 ml with the same mixture of solvents.

Reference solution (a). Dissolve 21.6 mg of *diclofenac sodium CRS* in a mixture of 30 volumes of mobile phase A and 70 volumes of mobile phase B and dilute to 50.0 ml with the same mixture of solvents.

Reference solution (b). Dilute 2.0 ml of the test solution to 10.0 ml with a mixture of 30 volumes of mobile phase A and 70 volumes of mobile phase B.

Reference solution (c). Mix 1.0 ml of reference solution (a) and 1.0 ml of reference solution (b) and dilute to 100.0 ml with a mixture of 30 volumes of mobile phase A and 70 volumes of mobile phase B.

Reference solution (d). Dissolve 4.0 mg of *aceclofenac impurity F CRS*, 2.0 mg of *aceclofenac impurity H CRS* and 2.0 mg of *diclofenac impurity A CRS* (aceclofenac impurity I) in a mixture of 30 volumes of mobile phase A and 70 volumes of mobile phase B and dilute to 10.0 ml with the same mixture of solvents.

Reference solution (e). Mix 1.0 ml of reference solution (b) and 1.0 ml of reference solution (d) and dilute to 100.0 ml with a mixture of 30 volumes of mobile phase A and 70 volumes of mobile phase B.

Column:

- *size*: *l* = 0.25 m, Ø = 4.6 mm,
- *stationary phase*: spherical *end-capped octadecylsilyl silica gel for chromatography R* (5 µm) with a pore size of 10 nm and a carbon loading of 19 per cent,
- *temperature*: 40 °C.

Mobile phase:

- *mobile phase A*: 1.12 g/l solution of *phosphoric acid R* adjusted to pH 7.0 using a 42 g/l solution of *sodium hydroxide R*,
- *mobile phase B*: *water R, acetonitrile R* (1:9 *V/V*),

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 25	70 → 50	30 → 50
25 - 30	50 → 20	50 → 80
30 - 50	20	80
50 - 52	20 → 70	80 → 30
52 - 65	70	30

Flow rate: 1.0 ml/min.

Detection: spectrophotometer at 275 nm.

Injection: 10 µl; inject the test solution and reference solutions (c) and (e).

Relative retention with reference to aceclofenac (retention time = about 14 min): impurity A = about 0.8; impurity G = about 1.3; impurity H = about 1.5; impurity I = about 2.3; impurity D = about 2.6; impurity B = about 2.7; impurity E = about 2.8; impurity C = about 3.0; impurity F = about 3.2.

System suitability: reference solution (c):

- *resolution*: minimum 5.0 between the peaks due to aceclofenac and to impurity A.

Limits:

- *impurity A*: not more than the area of the corresponding peak in the chromatogram obtained with reference solution (c) (0.2 per cent),
- *impurities B, C, D, E, G*: for each impurity, not more than the area of the peak due to aceclofenac in the chromatogram obtained with reference solution (e) (0.2 per cent),
- *impurity F*: not more than the area of the corresponding peak in the chromatogram obtained with reference solution (e) (0.2 per cent),
- *impurity H*: not more than the area of the corresponding peak in the chromatogram obtained with reference solution (e) (0.1 per cent),
- *impurity I*: not more than the area of the corresponding peak in the chromatogram obtained with reference solution (e) (0.1 per cent),
- *any other impurity*: not more than half the area of the peak due to aceclofenac in the chromatogram obtained with reference solution (e) (0.1 per cent),
- *total*: not more than 0.7 per cent,
- *disregard limit*: 0.1 times the area of the peak due to aceclofenac in the chromatogram obtained with reference solution (e) (0.02 per cent).

Heavy metals (*2.4.8*): maximum 10 ppm.

To 2.0 g in a silica crucible, add 2 ml of *sulphuric acid R* to wet the substance. Heat progressively to ignition and continue heating until an almost white or at most a greyish residue is obtained. Carry out the ignition at a temperature not exceeding 800 °C. Allow to cool. Add 3 ml of *hydrochloric acid R* and 1 ml of *nitric acid R*. Heat and evaporate slowly to dryness. Cool and add 1 ml of a 100 g/l solution of *hydrochloric acid R* and 10.0 ml of *distilled water R*. Neutralise with a 1.0 g/l solution of *ammonia R* using 0.1 ml of *phenolphthalein solution R* as indicator. Add 2.0 ml of a 60 g/l solution of *anhydrous acetic acid R* and dilute to 20 ml with *distilled water R*. 12 ml of the solution complies with limit test A. Prepare the standard using *lead standard solution (1 ppm Pb) R*.

Loss on drying (*2.2.32*): maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C.

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

ASSAY

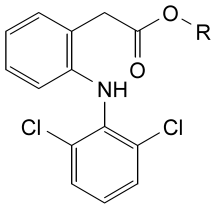
Dissolve 0.300 g in 40 ml of *methanol R*. Titrate with *0.1 M sodium hydroxide*, determining the end-point potentiometrically (*2.2.20*).

1 ml of *0.1 M sodium hydroxide* is equivalent to 35.42 mg of $C_{16}H_{13}Cl_2NO_4$.

STORAGE

In an airtight container, protected from light.

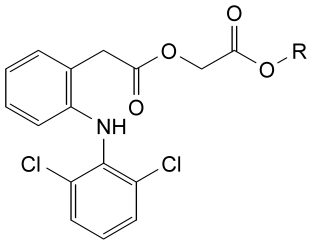
IMPURITIES



A. R = H: [2-[(2,6-dichlorophenyl)amino]phenyl]acetic acid (diclofenac),

B. R = CH_3: methyl [2-[(2,6-dichlorophenyl)amino]phenyl]acetate (methyl ester of diclofenac),

C. R = C_2H_5: ethyl [2-[(2,6-dichlorophenyl)amino]phenyl]acetate (ethyl ester of diclofenac),



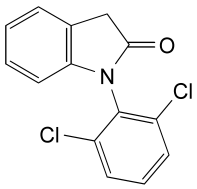
D. R = CH_3: methyl [[[2-[(2,6-dichlorophenyl)amino]phenyl]acetyl]oxy]acetate (methyl ester of aceclofenac),

E. R = C_2H_5: ethyl [[[2-[(2,6-dichlorophenyl)amino]phenyl]acetyl]oxy]acetate (ethyl ester of aceclofenac),

F. R = CH_2-C_6H_5: benzyl [[[2-[(2,6-dichlorophenyl)amino]phenyl]acetyl]oxy]acetate (benzyl ester of aceclofenac),

G. R = CH_2-CO_2H: [[[[[2-[(2,6-dichlorophenyl)amino]phenyl]acetyl]oxy]acetyl]oxy]acetic acid (acetic aceclofenac),

H. R = CH_2-CO-O-CH_2-CO_2H: [[[[[[[2-[(2,6-dichlorophenyl)amino]phenyl]acetyl]oxy]acetyl]oxy]acetyl]oxy]acetic acid (diacetic aceclofenac),

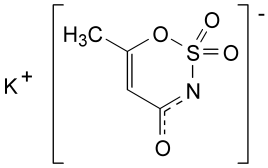


I. 1-(2,6-dichlorophenyl)-1,3-dihydro-2*H*-indol-2-one.

01/2008:1282
corrected 6.0

ACESULFAME POTASSIUM

Acesulfamum kalicum



$C_4H_4KNO_4S$ M_r 201.2
[55589-62-3]

DEFINITION

Potassium 6-methyl-1,2,3-oxathiazin-4-olate 2,2-dioxide.

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

CHARACTERS

Appearance: white or almost white, crystalline powder or colourless crystals.

Solubility: soluble in water, very slightly soluble in acetone and in ethanol (96 per cent).

IDENTIFICATION

First identification: A, C.

Second identification: B, C.

A. Infrared absorption spectrophotometry (*2.2.24*).
Comparison: *acesulfame potassium CRS*.

B. Thin-layer chromatography (*2.2.27*).
Test solution. Dissolve 5 mg of the substance to be examined in *water R* and dilute to 5 ml with the same solvent.
Reference solution (a). Dissolve 5 mg of *acesulfame potassium CRS* in *water R* and dilute to 5 ml with the same solvent.
Reference solution (b). Dissolve 5 mg of *acesulfame potassium CRS* and 5 mg of *saccharin sodium R* in *water R* and dilute to 5 ml with the same solvent.
Plate: *cellulose for chromatography R* as the coating substance.
Mobile phase: *concentrated ammonia R, acetone R, ethyl acetate R* (10:60:60 *V/V/V*).
Application: 5 µl as bands.
Development: twice over a path of 15 cm.
Drying: in a current of warm air.
Detection: examine in ultraviolet light at 254 nm.
System suitability: reference solution (b):
– the chromatogram shows 2 clearly separated bands.
Results: the principal band in the chromatogram obtained with the test solution is similar in position and size to the principal band in the chromatogram obtained with reference solution (a).

C. 0.5 ml of solution S (see Tests) gives reaction (b) of potassium (*2.3.1*).

TESTS

Solution S. Dissolve 10.0 g in *carbon dioxide-free water R* and dilute to 50 ml with the same solvent.

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

Acidity or alkalinity. To 20 ml of solution S add 0.1 ml of *bromothymol blue solution R1*. Not more than 0.2 ml of *0.01 M hydrochloric acid* or *0.01 M sodium hydroxide* is required to change the colour of the indicator.

Impurity A. Thin-layer chromatography (*2.2.27*).
Test solution. Dissolve 0.80 g of the substance to be examined in *water R* and dilute to 10 ml with the same solvent.
Reference solution (a). Dissolve 50 mg of *acetylacetamide R* (impurity A) in *water R* and dilute to 25 ml with the same solvent. To 5 ml of the solution add 45 ml of *water R* and dilute to 100 ml with *methanol R*.
Reference solution (b). To 10 ml of reference solution (a) add 1 ml of the test solution and dilute to 20 ml with *methanol R*.
Plate: *TLC silica gel plate R*.
Mobile phase: *water R, ethanol (96 per cent) R, ethyl acetate R* (2:15:74 *V/V/V*).
Application: 5 µl.