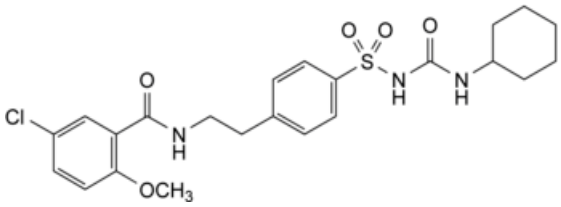
Edition: BP 2025 (Ph. Eur. 11.6 update)

Glibenclamide

General Notices

(Ph. Eur. monograph 0718)



$C_{23}H_{28}ClN_3O_5S$ 494.0 *10238-21-8*

Action and use

Inhibition of ATP-dependent potassium channels (sulfonylurea); treatment of diabetes mellitus.

Preparation

Glibenclamide Tablets

Ph Eur

DEFINITION

1-[[4-[2-[(5-Chloro-2-methoxybenzoyl)amino]ethyl]phenyl]sulfonyl]-3-cyclohexylurea.

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, sparingly soluble in methylene chloride, slightly soluble in ethanol (96 per cent) and in methanol.

It shows polymorphism (*5.9*).

IDENTIFICATION

First identification: C.

Second identification: A, B, D, E.

A. Melting point (2.2.14): 169 °C to 174 °C.
B. Ultraviolet and visible absorption spectrophotometry (2.2.25).

Test solution Dissolve 50.0 mg in methanol R, with the aid of ultrasound if necessary, and dilute to 50.0 mL with the same solvent. To 10.0 mL of the solution add 1.0 mL of a 103 g/L solution of hydrochloric acid R and dilute to 100.0 mL with methanol R.

Spectral range 230-350 nm.

Absorption maxima At 300 nm and a less intense maximum at 275 nm.

Specific absorbance at the absorption maxima:

— at 300 nm: 61 to 65;

— at 275 nm: 27 to 32.

C. Infrared absorption spectrophotometry (2.2.24).

Comparison glibenclamide CRS.

If the spectra obtained show differences, moisten separately the substance to be examined and the reference substance with methanol R, triturate, dry at 100-105 °C and record the spectra again.

D. Thin-layer chromatography (2.2.27).

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

Reference solution Dissolve 10 mg of glibenclamide CRS in a mixture of equal volumes of methanol R and methylene chloride R and dilute to 10 mL with the same mixture of solvents.

Plate TLC silica gel GF_{254} plate R.

Mobile phase ethanol (96 per cent) R, glacial acetic acid R, cyclohexane R, methylene chloride R (5:5:45:45 *V/V/V/V*).

Application 10 µL.

Development Over 1/2 of the plate.

Drying In air.

Detection Examine in ultraviolet light at 254 nm.

Results 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.

E. Dissolve 20 mg in 2 mL of sulfuric acid R. The solution is colourless and shows blue fluorescence in ultraviolet light at 365 nm. Dissolve 0.1 g of chloral hydrate R in the solution. After about 5 min, the colour changes to deep yellow and, after about 20 min, develops a brownish tinge.

TESTS

Related substances

Liquid chromatography (2.2.29). *Prepare the solutions immediately before use or store them at 5 °C for not more than 40 h.*

Test solution Dissolve 25.0 mg of the substance to be examined in *methanol R*, with the aid of ultrasound if necessary, and dilute to 10.0 mL with the same solvent.

Reference solution (a) Dissolve 3.0 mg of *glibenclamide impurity A CRS* and 3 mg of *glibenclamide impurity B CRS* in *methanol R* and dilute to 100.0 mL with the same solvent. Dilute 5.0 mL of the solution to 20.0 mL with *methanol R*.

Reference solution (b) Dilute 1.0 mL of the test solution to 100.0 mL with *methanol R*. Dilute 1.0 mL of this solution to 10.0 mL with *methanol R*.

Reference solution (c) Dissolve 12.5 mg of *glibenclamide for peak identification CRS* (containing impurity C) in *methanol R*, with the aid of ultrasound if necessary, and dilute to 5.0 mL with the same solvent.

Column:

— *size*: *l* = 0.10 m, *Ø* = 4.6 mm;

— *stationary phase*: spherical *base-deactivated end-capped octadecylsilyl silica gel for chromatography R* (3 µm);

— *temperature*: 35 °C.

Mobile phase:

— *mobile phase A*: mix 20 mL of a 100.0 g/L solution of *triethylamine R2* previously adjusted to pH 3.0 using *phosphoric acid R*, and 50 mL of *acetonitrile R*; dilute to 1000 mL with *water R*;

— *mobile phase B*: mobile phase A, *water R*, *acetonitrile R* (2:6.5:91.5 *V/V/V*);

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 15	45	55
15 - 30	45 → 5	55 → 95
30 - 40	5	95

Flow rate 0.8 mL/min.

Detection Spectrophotometer at 230 nm.

Injection 10 µL.

Identification of impurities Use the chromatogram obtained with reference solution (a) to identify the peaks due to impurities A and B; use the chromatogram supplied with *glibenclamide for peak identification CRS* and the chromatogram obtained with reference solution (c) to identify the peak due to impurity C.

Relative retention With reference to glibenclamide (retention time = about 5 min): impurity A = about 0.5; impurity B = about 0.6; impurity C = about 0.7.

System suitability Reference solution (a):

— *resolution*: minimum 2.0 between the peaks due to impurities A and B.

Limits:

— *correction factor*: for the calculation of content, multiply the peak area of impurity C by 1.8;

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

— *impurity C*: not more than 1.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (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 (b) (0.10 per cent);

— *total*: 0.8 per cent;

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

Loss on drying (*2.2.32*)

Maximum 1.0 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

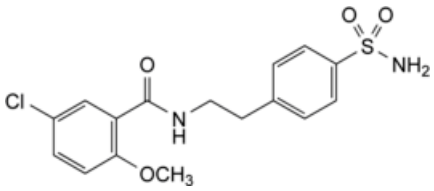
Dissolve 0.400 g with heating in 100 mL of *ethanol (96 per cent) R*. Titrate with *0.1 M sodium hydroxide*, determining the end-point potentiometrically (*2.2.20*).

1 mL of *0.1 M sodium hydroxide* is equivalent to 49.40 mg of $C_{23}H_{28}ClN_3O_5S$.

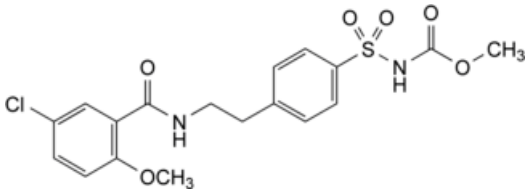
IMPURITIES

Specified impurities *A, C*.

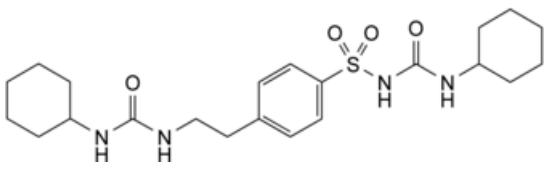
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical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



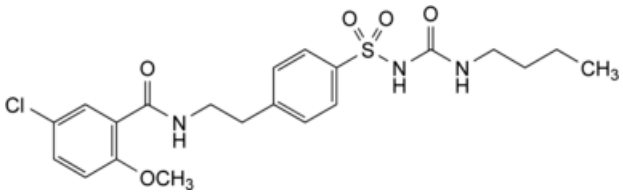
A. 5-chloro-2-methoxy-*N*-[2-(4-sulfamoylphenyl)ethyl]benzamide,



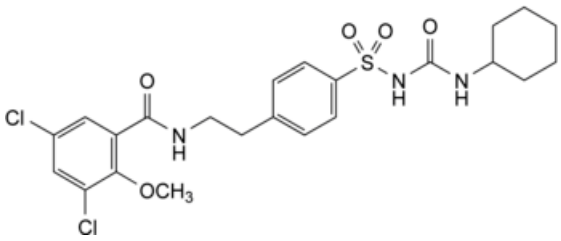
B. methyl [[4-[2-[(5-chloro-2-methoxybenzoyl)amino]ethyl]phenyl]sulfonyl]carbamate,



C. 1-cyclohexyl-3-[[4-[2-[(cyclohexylcarbamoyl)amino]ethyl]phenyl]sulfonyl]urea,



D. 1-butyl-3-[[4-[2-[(5-chloro-2-methoxybenzoyl)amino]ethyl]phenyl]sulfonyl]urea,



E. 1-cyclohexyl-3-[[4-[2-[(3,5-dichloro-2-methoxybenzoyl)amino]ethyl]phenyl]sulfonyl]urea.

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