FUNCTIONALITY-RELATED CHARACTERISTICS

This section provides information on characteristics that are recognised as being relevant control parameters for one or more functions of the substance when used as an excipient (see chapter 5.15). This section is a non-mandatory part of the monograph and it is not necessary to verify the characteristics to demonstrate compliance. Control of these characteristics can however contribute to the quality of a medicinal product by improving the consistency of the manufacturing process and the performance of the medicinal product during use. Where control methods are cited, they are recognised as being suitable for the purpose, but other methods can also be used. Wherever results for a particular characteristic are reported, the control method must be indicated.

The following characteristics may be relevant for microcrystalline cellulose and carmellose sodium used as a suspending agent.

Apparent viscosity (*2.2.10*) : 60 per cent to 140 per cent of the nominal value.

Calculate the quantity (*x* g) needed to prepare exactly 600 g of a dispersion of the stated percentage *m/m* (dried substance). To (600 - *x*) g of *water R* at 23-25 °C contained in a 1000 mL high-speed blender bowl add *x* g of the substance to be examined and stir at reduced speed, taking care to avoid contacting the sides of the bowl with the powder. Continue stirring at low speed for 15 s after the addition of the powder and then stir at 18 000 r/min for exactly 2 min.

Determine the viscosity with a suitable relative rotational viscometer under the following conditions:

– spindle: as appropriate;
– speed: 20 r/min.

Immerse the spindle into the suspension immediately after preparation, switch on the rotation spindle after 30 s, after a further 30 s take scale readings and calculate the viscosity according to the viscometer manual.

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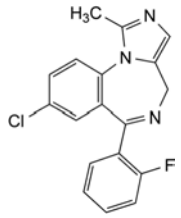
corrected 6.0

MIDAZOLAM

Midazolamum



$C_{18}H_{13}ClFN_3$ M_r 325.8
[59467-70-8]

DEFINITION

8-Chloro-6-(2-fluorophenyl)-1-methyl-4*H*-imidazo[1,5-*a*][1,4]-benzodiazepine.

Content: 98.5 per cent to 101.5 per cent (dried substance).

CHARACTERS

Appearance: white or yellowish, crystalline powder.

Solubility: practically insoluble in water, freely soluble in acetone and in ethanol (96 per cent), soluble in methanol.

IDENTIFICATION

First identification: B.

Second identification: A, C, D, E.

A. Melting point (*2.2.14*): 161 °C to 164 °C.

B. Infrared absorption spectrophotometry (*2.2.24*).
Comparison: *midazolam CRS*.

C. Examine the chromatograms obtained in the test for impurity C.
Results: the principal spot in the chromatogram obtained with test solution (b) is similar in position and size to the principal spot in the chromatogram obtained with reference solution (b).

D. Mix 90 mg with 0.30 g of *anhydrous sodium carbonate R* and ignite in a crucible until an almost white residue is obtained (normally in less than 5 min). Allow to cool and dissolve the residue in 5 mL of *dilute nitric acid R*. Filter (the filtrate is also used in identification test E). Add 1.0 mL of the filtrate to a freshly prepared mixture of 0.1 mL of *alizarin S solution R* and 0.1 mL of *zirconyl nitrate solution R*. Mix, allow to stand for 5 min and compare the colour of the solution with that of a blank prepared in the same manner. The test solution is yellow and the blank solution is red.

E. To 1 mL of the filtrate obtained in identification test D add 1 mL of *water R*. The solution gives reaction (a) of chlorides (*2.3.1*).

TESTS

Appearance of solution. The solution is clear (*2.2.1*) and not more intensely coloured than reference solution Y_6 (*2.2.2, Method II*).

Dissolve 0.1 g in *0.1 M hydrochloric acid* and dilute to 10 mL with the same acid.

Related substances. Liquid chromatography (*2.2.29*).

Test solution. Dissolve 50.0 mg of the substance to be examined in *methanol R* and dilute to 50.0 mL with the same solvent.

Reference solution (a). 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 (b). Dissolve the contents of a vial of *midazolam for system suitability CRS* (containing impurities A, B, E, G and H) in 1.0 mL of *methanol R*.

Column:

– *size*: *l* = 0.25 m, Ø = 4.0 mm,
– *stationary phase*: *octylsilyl silica gel for chromatography R* (5 µm).

Mobile phase: prepare a solution containing 7.7 g/L of *ammonium acetate R* and 10 mL/l of *tetrabutylammonium hydroxide solution (400 g/L) R* and adjust to pH 5.3 with *glacial acetic acid R*. Mix 44 volumes of this solution with 56 volumes of *methanol R*.

Flow rate: 1.0 mL/min.

Detection: spectrophotometer at 254 nm.

Injection: 10 µL.

Run time: 2.5 times the retention time of midazolam.

Relative retention with reference to midazolam (retention time = about 17 min): impurity I = about 0.25; impurity J (2 peaks) = about 0.3; impurity D = about 0.4; impurity E = about 0.5; impurity F = about 0.7; impurity A = about 0.9; impurity G = about 1.2; impurity H = about 1.9; impurity B = about 2.2.

System suitability: reference solution (b):

– *peak-to-valley ratio*: minimum 3.0 where H_p = height above the baseline of the peak due to impurity A and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to midazolam.

Limits:

– *correction factors*: for the calculation of content, multiply the peak areas of the following impurities by the corresponding correction factor: impurity A = 2; impurity E = 2; impurity H = 1.7;
– *impurity B*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 per cent),

– *impurities A, G*: 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) (0.1 per cent);
– *total*: not more than 3 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.3 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).

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

Test solution (a). Dissolve 0.20 g of the substance to be examined in *ethanol (96 per cent) R* and dilute to 5 mL with the same solvent.

Test solution (b). Dilute 1 mL of test solution (a) to 50 mL with *ethanol (96 per cent) R*.

Reference solution (a). Dissolve the contents of a vial of *midazolam impurity C CRS* in 2.0 mL of *methanol R*.

Reference solution (b). Dissolve 8 mg of *midazolam CRS* in *ethanol (96 per cent) R* and dilute to 10 mL with the same solvent.

Reference solution (c). Dissolve 40 mg of the substance to be examined in 1 mL of reference solution (a).

Plate: *TLC silica gel F_{254} plate R*.

Mobile phase: *glacial acetic acid R, water R, methanol R, ethyl acetate R* (2:15:20:80 *V/V/V/V*).

Application: 5 µL.

Development: over 2/3 of the plate.

Drying: in air.

Detection: examine in ultraviolet light at 254 nm.

System suitability: reference solution (c):

– the chromatogram shows 2 clearly separated spots.

Limit:

– *impurity C*: any spot due to impurity C in the chromatogram obtained with test solution (a) is not more intense than the spot in the chromatogram obtained with reference solution (a) (0.1 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 for 2 h.

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

ASSAY

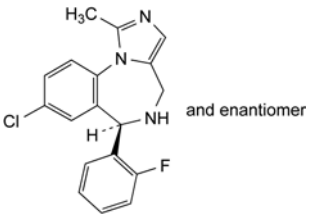
Dissolve 0.120 g in 30 mL of *anhydrous acetic acid R* and add 20 mL of *acetic anhydride R*. Titrate with *0.1 M perchloric acid* to the 2nd point of inflexion, determining the end-point potentiometrically (*2.2.20*).

1 mL of *0.1 M perchloric acid* is equivalent to 16.29 mg of $C_{18}H_{13}ClFN_3$.

IMPURITIES

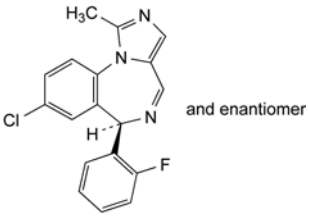
Specified impurities: *A, B, C, G*.

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*): *D, E, F, H, I, J*.



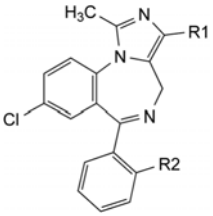
and enantiomer

A. (6*RS*)-8-chloro-6-(2-fluorophenyl)-1-methyl-5,6-dihydro-4*H*-imidazo[1,5-*a*][1,4]benzodiazepine,



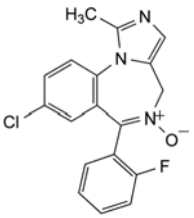
and enantiomer

B. (6*RS*)-8-chloro-6-(2-fluorophenyl)-1-methyl-6*H*-imidazo-[1,5-*a*][1,4]benzodiazepine,

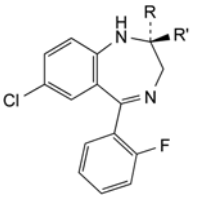


C. R1 = CO_2H, R2 = F: 8-chloro-6-(2-fluorophenyl)-1-methyl-4*H*-imidazo[1,5-*a*][1,4]benzodiazepine-3-carboxylic acid,

G. R1 = R2 = H: 8-chloro-1-methyl-6-phenyl-4*H*-imidazo-[1,5-*a*][1,4]benzodiazepine (desfluoromidazolam),



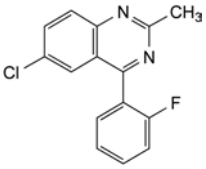
D. 8-chloro-6-(2-fluorophenyl)-1-methyl-4*H*-imidazo-[1,5-*a*][1,4]benzodiazepine 5-oxide,



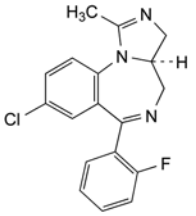
and enantiomer

E. R = CH_2-NH_2, R′ = H: [(2*RS*)-7-chloro-5-(2-fluorophenyl)-2,3-dihydro-1*H*-1,4-benzodiazepine-2-yl]methanamine,

F. R + R′ = O: 7-chloro-5-(2-fluoropheny)-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one (1-des[(diethylamino)ethyl]flurazepam),

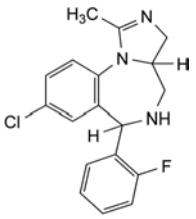


H. 6-chloro-4-(2-fluorophenyl)-2-methylquinazoline,



and enantiomer

I. (3a*RS*)-8-chloro-6-(2-fluorophenyl)-1-methyl-3a,4-dihydro-3*H*-imidazo[1,5-*a*][1,4]benzodiazepine,



J. 8-chloro-6-(2-fluorophenyl)-1-methyl-3a,4,5,6-tetrahydro-3*H*-imidazo[1,5-*a*][1,4]benzodiazepine.

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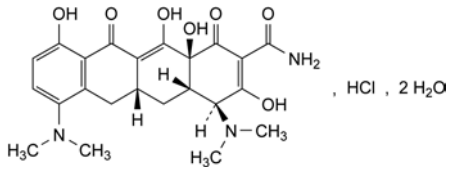
corrected 7.0

MINOCYCLINE HYDROCHLORIDE DIHYDRATE

Minocyclini hydrochloridum dihydricum



$C_{23}H_{28}ClN_3O_7,2H_2O$ M_r 530.0
[13614-98-7]

DEFINITION

(4*S*,4a*S*,5a*R*,12a*S*)-4,7-Bis(dimethylamino)-3,10,12,12a-tetrahydroxy-1,11-dioxo-1,4,4a,5,5a,6,11,12a-octahydrotetracene-2-carboxamide hydrochloride dihydrate.

Semi-synthetic product derived from a fermentation product.

Content: 96.0 per cent to 102.5 per cent (anhydrous substance).

CHARACTERS

Appearance: yellow, hygroscopic, crystalline powder.

Solubility: sparingly soluble in water, slightly soluble in ethanol (96 per cent). It dissolves in solutions of alkali hydroxides and carbonates.

IDENTIFICATION

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

Test solution. Dissolve 5 mg of the substance to be examined in *methanol R* and dilute to 10 mL with the same solvent.

Reference solution (a). Dissolve 5 mg of *minocycline hydrochloride CRS* in *methanol R* and dilute to 10 mL with the same solvent.

Reference solution (b). Dissolve 5 mg of *minocycline hydrochloride CRS* and 5 mg of *oxytetracycline hydrochloride CRS* in *methanol R* and dilute to 10 mL with the same solvent.

Plate: *TLC octadecylsilyl silica gel F_{254} plate R*.

Mobile phase: mix 20 volumes of *acetonitrile R*, 20 volumes of *methanol R* and 60 volumes of a 63 g/L solution of *oxalic acid R* previously adjusted to pH 2 with *concentrated ammonia R*.

Application: 1 µL

Development: over 3/4 of the plate.

Drying: in air.

Detection: examine in ultraviolet light at 254 nm.

System suitability: reference solution (b):

– the chromatogram shows 2 clearly separated spots.

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 reference solution (a).

B. To about 2 mg add 5 mL of *sulfuric acid R*. A bright yellow colour develops. Add 2.5 mL of *water R* to the solution. The solution becomes pale yellow.

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

TESTS

Solution S. Dissolve 0.200 g in *carbon dioxide-free water R* and dilute to 20.0 mL with the same solvent.

Appearance of solution. The solution is clear (*2.2.1*) and its absorbance (*2.2.25*) at 450 nm using a 1 cm cell is not greater than 0.23.

Dilute 1.0 mL of solution S to 10.0 mL with *water R*.

pH (*2.2.3*): 3.5 to 4.5 for solution S.

Light-absorbing impurities. *Carry out the measurement within 1 h of preparing solution S.*

The absorbance (*2.2.25*) of solution S measured at 560 nm is not greater than 0.06.

Related substances. Liquid chromatography (*2.2.29*).

Carry out the test protected from bright light. Store the solutions at a temperature of 2-8 °C and use them within 3 h of preparation.

Test solution (a). Dissolve 25.0 mg of the substance to be examined in the mobile phase and dilute to 100.0 mL with the mobile phase.

Test solution (b). Dilute 10.0 mL of test solution (a) to 20.0 mL with the mobile phase.

Reference solution (a). Dissolve 12.5 mg of *minocycline hydrochloride CRS* in the mobile phase and dilute to 100.0 mL with the mobile phase.

Reference solution (b). Dilute 2.0 mL of test solution (a) to 100.0 mL with the mobile phase.

Reference solution (c). Dilute 1.2 mL of test solution (a) to 100.0 mL with the mobile phase.

Reference solution (d). Dissolve 10 mg of *minocycline hydrochloride CRS* in 1 mL of *water R*. Boil the solution on a water-bath for 20 min. Dilute to 25 mL with the mobile phase.

Column:

– *size*: *l* = 0.20 m, Ø = 4.6 mm;

– *stationary phase*: *octylsilyl silica gel for chromatography R* (5 µm).

Mobile phase: mix 25 volumes of a 4 g/L solution of *sodium edetate R*, 27 volumes of *dimethylformamide R* and 50 volumes of a 28 g/L solution of *ammonium oxalate R*, and adjust to pH 7.0 with *tetrabutylammonium hydroxide solution (104 g/L) R*.

Flow rate: 1 mL/min.

Detection: spectrophotometer at 280 nm.

Injection: 20 µL of test solution (a) and reference solutions (a), (b), (c) and (d).

Run time: 1.5 times the retention time of minocycline.

System suitability:

– *resolution*: minimum 2.0 between the peaks due to impurity A and minocycline in the chromatogram obtained with reference solution (d);

– *number of theoretical plates*: minimum 3000, calculated for the peak due to minocycline in the chromatogram obtained with reference solution (a).