ASSAY

Dissolve 0.350 g in 75 mL of *anhydrous acetic acid R*, with slight heating if necessary. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (*2.2.20*). Carry out a blank titration.

1 mL of *0.1 M perchloric acid* is equivalent to 47.91 mg of $C_{18}H_{15}Cl_4N_3O_4$.

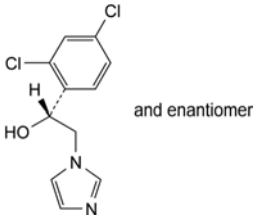
STORAGE

Protected from light.

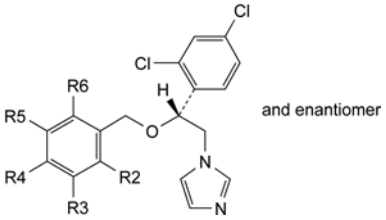
IMPURITIES

Specified impurities: A, B, C, D, E, F, 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*): *H, I.*



A. (1*RS*)-1-(2,4-dichlorophenyl)-2-(1*H*-imidazol-1-yl)ethanol,



B. R2 = R3 = R5 = R6 = H, R4 = Cl: 1-[(2*RS*)-2-[(4-chlorobenzyl)oxy]-2-(2,4-dichlorophenyl)ethyl]-1*H*-imidazole,

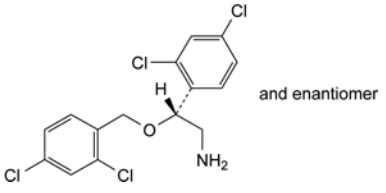
D. R2 = R6 = Cl, R3 = R4 = R5 = H: 1-[(2*RS*)-2-[(2,6-dichlorobenzyl)oxy]-2-(2,4-dichlorophenyl)ethyl]-1*H*-imidazole,

F. R2 = R5 = R6 = H, R3 = R4 = Cl: 1-[(2*RS*)-2-[(3,4-dichlorobenzyl)oxy]-2-(2,4-dichlorophenyl)ethyl]-1*H*-imidazole,

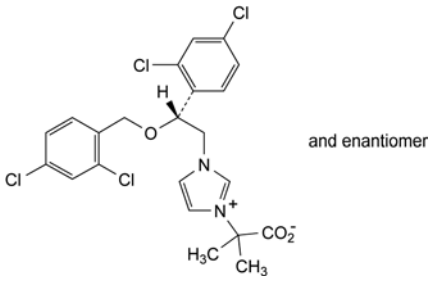
G. R2 = R5 = Cl, R3 = R4 = R6 = H: 1-[(2*RS*)-2-[(2,5-dichlorobenzyl)oxy]-2-(2,4-dichlorophenyl)ethyl]-1*H*-imidazole,

H. R2 = R3 = R4 = R5 = R6 = H: 1-[(2*RS*)-2-benzyloxy-2-(2,4-dichlorophenyl)ethyl]-1*H*-imidazole,

I. R2 = Cl, R3 = R4 = R5 = R6 = H: 1-[(2*RS*)-2-[(2-chlorobenzyl)oxy]-2-(2,4-dichlorophenyl)ethyl]-1*H*-imidazole,



C. (2*RS*)-2-[(2,4-dichlorobenzyl)oxy]-2-(2,4-dichlorophenyl)ethanamine,



E. 2-[1-[(2*RS*)-2-[(2,4-dichlorobenzyl)oxy]-2-(2,4-dichlorophenyl)ethyl]-1*H*-imidazol-3-io]-2-methylpropanoate.

01/2008:2050
corrected 7.0

MICROCRYSTALLINE CELLULOSE AND CARMELLOSE SODIUM

Cellulosum microcristallinum et carmellosum natricum

DEFINITION

Colloid-forming, powdered mixture of *Microcrystalline Cellulose (0316)* with 5 per cent to 22 per cent of *Carmellose sodium (0472)*.

Content: 75.0 per cent to 125.0 per cent of the nominal amount of carmellose sodium (dried substance).

CHARACTERS

Appearance: white or off-white, coarse or fine powder.

Solubility: dispersible in water producing a white, opaque colloidal dispersion; practically insoluble in organic solvents and in dilute acids.

IDENTIFICATION

A. Mix 6 g with 300 mL of *water R* and stir at 18 000 r/min for 5 min. A white opaque dispersion is obtained which does not produce a supernatant liquid.

B. Add several drops of the dispersion obtained in identification A to a 10 per cent *V/V* solution of *aluminium chloride R*. Each drop forms a white, opaque globule which does not disperse on standing.

C. Add 2 mL of *iodinated potassium iodide solution R* to the dispersion obtained in test A. No blue or purplish colour is produced.

D. It complies with the limits of the assay.

TESTS

Solubility. Add 50 mg to 10 mL of *ammoniacal solution of copper tetrammine R* and shake. It dissolves completely leaving no residue.

pH (*2.2.3*): 6.0 to 8.0 for the dispersion obtained in identification A.

Loss on drying (*2.2.32*): maximum 8.0 per cent, determined on 1.000 g by drying in an oven at 105 °C.

Sulfated ash (*2.4.14*): maximum 7.4 per cent, determined on 2.0 g.

ASSAY

Heat 2.00 g with 75 mL of *anhydrous acetic acid R* under a reflux condenser for 2 h, cool and titrate with *0.1 M perchloric acid*, determining the end point potentiometrically (*2.2.20*).

1 mL of *0.1 M perchloric acid* is equivalent to 29.6 mg of carmellose sodium.

LABELLING

The label states the nominal percentage *m/m* of carmellose sodium.

Monographs M

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:

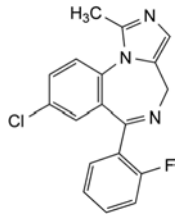
– spindle: as appropriate;
– speed: 20 r/min.

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.

01/2008:0936
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),