Relative retention with reference to thioridazine (retention time = about 30 min): impurity D = about 0.1; impurity A = about 0.3; impurity C = about 0.4; impurity B = about 0.5; impurity E = about 0.6; impurity F = about 0.9.

System suitability: reference solution (b):

– *resolution*: minimum 3.5 between the peaks due to impurities C and B.

Limits:

– *correction factors*: for the calculation of content, multiply the peak areas of the following impurities by the corresponding correction factor: impurity A = 1.9; impurity B = 2.4; impurity C = 0.5; impurity D = 1.5;

– *impurities A, B, C, D, E*: 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 5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.5 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).

Heavy metals (*2.4.8*): maximum 20 ppm.

Dissolve 1.0 g in 20 ml of *water R*. 12 ml of the solution complies with test A. Prepare the reference solution 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 for 4 h.

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

ASSAY

Dissolve 0.300 g in a mixture of 10 ml of *anhydrous acetic acid R* and 60 ml of *acetic anhydride R*. 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 40.70 mg of $C_{21}H_{27}ClN_2S_2$.

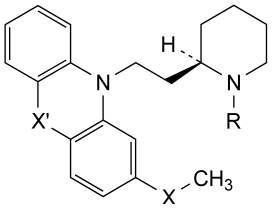
STORAGE

Protected from light.

IMPURITIES

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

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*): *F*.



and enantiomer

A. R = CH_3, X = X′ = SO_2: 10-[2-[(2*RS*)-1-methylpiperidin-2-yl]ethyl]-2-(methylsulphonyl)-10*H*-phenothiazine 5,5-dioxide,

B. R = CH_3, X = SO, X′ = S: 10-[2-[(2*RS*)-1-methylpiperidin-2-yl]ethyl]-2-(methylsulphinyl)-10*H*-phenothiazine,

C. R = CH_3, X = S, X′ = SO: 10-[2-[(2*RS*)-1-methylpiperidin-2-yl]ethyl]-2-(methylsulphanyl)-10*H*-phenothiazine 5-oxide,

D. R = CH_3, X = X′ = SO: 10-[2-[(2*RS*)-1-methylpiperidin-2-yl]ethyl]-2-(methylsulphinyl)-10*H*-phenothiazine 5-oxide,

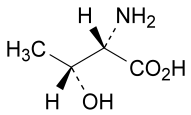
E. R = CH_3, X = SO_2, X′ = S: 10-[2-[(2*RS*)-1-methylpiperidin-2-yl]ethyl]-2-(methylsulphonyl)-10*H*-phenothiazine,

F. R = H, X = X′ = S: 2-(methylsulphanyl)-10-[2-[(2*RS*)-piperidin-2-yl]ethyl]-10*H*-phenothiazine.

01/2008:1049
corrected 6.0

THREONINE

Threoninum



$C_4H_9NO_3$ M_r 119.1
[72-19-5]

DEFINITION

Threonine contains not less than 99.0 per cent and not more than the equivalent of 101.0 per cent of (2*S*,3*R*)-2-amino-3-hydroxybutanoic acid, calculated with reference to the dried substance.

CHARACTERS

A white or almost white, crystalline powder or colourless crystals, soluble in water, practically insoluble in alcohol.

IDENTIFICATION

First identification: A, B.

Second identification: A, C, D.

A. It complies with the test for specific optical rotation (see Tests).

B. Examine by infrared absorption spectrophotometry (*2.2.24*), comparing with the spectrum obtained with *threonine CRS*. Examine the substances prepared as discs.

C. Examine the chromatograms obtained in the test for ninhydrin-positive substances. The principal spot in the chromatogram obtained with test solution (b) is similar in position, colour and size to the principal spot in the chromatogram obtained with reference solution (a).

D. Mix 1 ml of a 2 g/l solution of the substance to be examined with 1 ml of a 20 g/l solution of *sodium periodate R*. Add 0.2 ml of *piperidine R* and 0.1 ml of a 25 g/l solution of *sodium nitroprusside R*. A blue colour develops that changes to yellow after a few minutes.

TESTS

Solution S. Dissolve 2.5 g in *carbon dioxide-free water R* and dilute to 100 ml with the same solvent.

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

pH (*2.2.3*). The pH of solution S is 5.0 to 6.5.

Specific optical rotation (*2.2.7*). Dissolve 1.50 g in *water R* and dilute to 25.0 ml with the same solvent. The specific optical rotation is – 27.6 to – 29.0, calculated with reference to the dried substance.

Ninhydrin-positive substances. Examine by thin-layer chromatography (*2.2.27*), using a *TLC silica gel plate R*.

Test solution (a). Dissolve 0.10 g of the substance to be examined in *dilute hydrochloric acid R* and dilute to 10 ml with the same acid.

Test solution (b). Dilute 1 ml of test solution (a) to 50 ml with *water R*.

Reference solution (a). Dissolve 10 mg of *threonine CRS* in a 1 per cent *V/V* solution of *hydrochloric acid R* and dilute to 50 ml with the same acid solution.

Reference solution (b). Dilute 5 ml of test solution (b) to 20 ml with *water R*.

Reference solution (c). Dissolve 10 mg of *threonine CRS* and 10 mg of *proline CRS* in a 1 per cent *V/V* solution of *hydrochloric acid R* and dilute to 25 ml with the same acid solution.

Apply to the plate 5 µl of each solution. Allow the plate to dry in air. Develop over a path of 15 cm using a mixture of 20 volumes of *glacial acetic acid R*, 20 volumes of *water R* and 60 volumes of *butanol R*. Allow the plate to dry in air, spray with *ninhydrin solution R* and heat at 100 °C to 105 °C for 15 min. Any spot in the chromatogram obtained with test solution (a), apart from the principal spot, is not more intense than the spot in the chromatogram obtained with reference solution (b) (0.5 per cent). The test is not valid unless the chromatogram obtained with reference solution (c) shows two clearly separated principal spots.

Chlorides (*2.4.4*). Dilute 10 ml of solution S to 15 ml with *water R*. The solution complies with the limit test for chlorides (200 ppm).

Sulphates (*2.4.13*). Dissolve 0.5 g in *distilled water R* and dilute to 15 ml with the same solvent. The solution complies with the limit test for sulphates (300 ppm).

Ammonium (*2.4.1*). 0.10 g complies with limit test B for ammonium (200 ppm). Prepare the standard using 0.2 ml of *ammonium standard solution (100 ppm NH_4) R*.

Iron (*2.4.9*). In a separating funnel, dissolve 1.0 g in 10 ml of *dilute hydrochloric acid R*. Shake with three quantities, each of 10 ml, of *methyl isobutyl ketone R1*, shaking for 3 min each time. To the combined organic layers add 10 ml of *water R* and shake for 3 min. The aqueous layer complies with the limit test for iron (10 ppm).

Heavy metals (*2.4.8*). 2.0 g complies with limit test C for heavy metals (10 ppm). Prepare the standard using 2 ml of *lead standard solution (10 ppm Pb) R*.

Loss on drying (*2.2.32*). Not more than 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C.

Sulphated ash (*2.4.14*). Not more than 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.100 g in 5 ml of *anhydrous formic acid R*. Add 30 ml of *anhydrous acetic acid R*. 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 11.91 mg of $C_4H_9NO_3$.

STORAGE

Store protected from light.

01/2008:0865

THYME

Thymi herba

DEFINITION

Whole leaves and flowers separated from the previously dried stems of *Thymus vulgaris* L. or *Thymus zygis* L. or a mixture of both species.

Content:

– *essential oil*: minimum 12 ml/kg (anhydrous drug);
– *sum of the contents of thymol and carvacrol* (both $C_{10}H_{14}O$; M_r 150.2): minimum 40 per cent in the essential oil.

CHARACTERS

Strong aromatic odour reminiscent of thymol.

IDENTIFICATION

A. The leaf of *Thymus vulgaris* is usually 4 mm to 12 mm long and up to 3 mm wide, sessile or with a very short petiole. The lamina is tough, entire, lanceolate to ovate, covered on both surfaces by a grey or greenish-grey indumentum; the edges are markedly rolled up towards the abaxial surface. The midrib is depressed on the adaxial surface and is very prominent on the abaxial surface. The calyx is green, often with violet spots and is tubular; at the end are 2 lips of which the upper one is bent back and at the end has 3 lobes, the lower is longer and has 2 hairy teeth. After flowering, the calyx tube is closed by a crown of long, stiff hairs. The corolla, about twice as long as the calyx, is usually brownish in the dry state and is slightly bilabiate.

The leaf of *Thymus zygis* is usually 1.7 mm to 6.5 mm long and 0.4 mm to 1.2 mm wide; it is acicular to linear-lanceolate and the edges are markedly rolled towards the abaxial surface. Both surfaces of the lamina are green to greenish-grey and the midrib is sometimes violet; the edges, in particular at the base, have long, white hairs. The dried flowers are very similar to those of *Thymus vulgaris*.

B. Reduce to a powder (355) (*2.9.12*). The powder of both species is greyish-green or greenish-brown. Examine under a microscope using *chloral hydrate solution R*. The epidermises of the leaves have cells with anticlinal walls which are sinuous and beaded and the stomata are diacytic (*2.8.3*); numerous secretory trichomes made up of 12 secretory cells, the cuticle of which is generally raised by the secretion to form a globular to ovoid bladder-like covering; the glandular trichomes have a unicellular stalk and a globular to ovoid head; the covering trichomes of the adaxial surface are common