It has the macroscopic and microscopic characters described under identification tests A and B.

IDENTIFICATION

A. The fruit of sweet fennel is a cremocarp of almost cylindrical shape with a rounded base and a narrowed summit crowned with a large stylopod. It is generally 3 mm to 12 mm long and 3 mm to 4 mm wide. The mericarps, usually free, are glabrous. Each bears five prominent slightly carenated ridges. When cut transversely, four vittae on the dorsal surface and two on the commissural surface may be seen with a lens.

B. Reduce to a powder (355). The powder is greyish-brown to greyish-yellow. Examine under a microscope using *chloral hydrate solution R*. The powder shows the following diagnostic characters: yellow fragments of wide secretory canals, often made up of yellowish-brown-walled polygonal secretory cells, frequently associated with a layer of thin-walled transversely elongated cells 2 µm to 9 µm wide, having a parquetry arrangement; reticulate parenchyma of the mesocarp; numerous fibre bundles from the ridges, often accompanied by narrow spiral vessels; very numerous endosperm fragments containing aleurone grains and very small calcium oxalate microrosette crystals, as well as some fibre bundles from the carpophore.

C. Examine by thin-layer chromatography (*2.2.27*), using *silica gel* GF_{254} *R* as the coating substance.

Test solution. Shake 0.3 g of the freshly powdered drug (1400) with 5.0 ml of *methylene chloride R* for 15 min. Filter and carefully evaporate the filtrate to dryness on a water-bath at 60 °C. Dissolve the residue in 0.5 ml of *toluene R*.

Reference solution. Dissolve 60 µl of *anethole R* in 5.0 ml of *hexane R*.

Apply separately to the plate, as bands 20 mm by 3 mm, 10 µl of each solution. Develop over a path of 10 cm using a mixture of 20 volumes of *hexane R* and 80 volumes of *toluene R*. Allow the plate to dry in air and examine in ultraviolet light at 254 nm. The chromatograms show in the central part a quenching zone corresponding to anethole. Spray the plate with *sulphuric acid R* and heat at 140 °C for 5 min. Examine in daylight. The chromatograms show in the central part a violet band corresponding to anethole. The chromatogram obtained with the test solution also shows a reddish-brown zone in its upper third (terpenes).

TESTS

Estragole and fenchone. The essential oil obtained in the assay contains not more than 10.0 per cent of estragole and not more than 7.5 per cent of fenchone.

Proceed as described in the assay for anethole, using the following reference solution.

Reference solution. Dissolve 5 mg of *estragole R* and 5 mg of *fenchone R* in 0.5 ml of *xylene R*.

Determine the contents of estragole and fenchone by normalisation.

Foreign matter (*2.8.2*). Not more than 1.5 per cent of peduncles and not more than 1.5 per cent of other foreign matter.

Water (*2.2.13*). Not more than 80 ml/kg, determined by distillation on 20.0 g of the powdered drug (710).

Total ash (*2.4.16*). Not more than 10.0 per cent.

ASSAY

Essential oil. Carry out the determination of essential oils in vegetable drugs (*2.8.12*). Use a 500 ml round-bottomed flask and 200 ml of *water R* as the distillation liquid. Reduce the drug to a coarse powder (1400) and immediately use 10.0 g for the determination. Introduce 0.50 ml of *xylene R* in the graduated tube. Distil at a rate of 2 ml/min to 3 ml/min for 2 h.

Anethole. Examine by gas chromatography (*2.2.28*).

Test solution. Dilute the mixture of essential oil and *xylene R* obtained in the determination of the essential oil to 5.0 ml with *xylene R* and by rinsing the apparatus.

Reference solution. Dissolve 5 mg of *anethole R* in 0.5 ml of *xylene R*.

The chromatographic procedure may be carried out using:

– a capillary column 30 m to 60 m long and 0.3 mm in internal diameter coated with *macrogol 20 000 R*,

– *nitrogen for chromatography R* as the carrier gas at a flow rate of 0.40 ml/min and split at a ratio of 1 to 200,

– a flame-ionisation detector,

maintaining the temperature of the column at 60 °C for 4 min, then raising the temperature linearly at a rate of 5 °C per minute to 170 °C and maintaining at 170 °C for 15 min and maintaining the temperature of the injection port at 220 °C and that of the detector at 270 °C.

Inject 1 µl of each solution. Determine the content of anethole by normalisation.

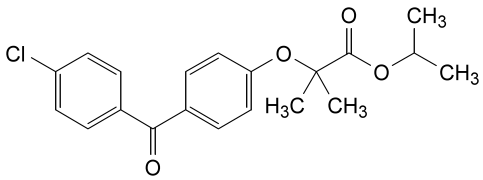
STORAGE

Store protected from light and moisture.

01/2005:1322

FENOFIBRATE

Fenofibratum



$C_{20}H_{21}ClO_4$ M_r 360.8

DEFINITION

Fenofibrate contains not less than 98.5 per cent and not more than the equivalent of 101.0 per cent of 1-methylethyl 2-[4-(4-chlorobenzoyl)phenoxy]-2-methylpropanoate, calculated with reference to the dried substance.

CHARACTERS

A white or almost white, crystalline powder, practically insoluble in water, very soluble in methylene chloride, slightly soluble in alcohol.

IDENTIFICATION

A. Melting point (*2.2.14*): 79 °C to 82 °C.

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

TESTS

Solution S. To 5.0 g, add 25 ml of *distilled water R* and heat at 50 °C for 10 min. Cool and dilute to 50.0 ml with the same solvent. Filter. Use the filtrate as solution S.

Appearance of solution. Dissolve 0.50 g in *acetone R* and dilute to 10.0 ml with the same solvent. The solution is clear (*2.2.1*) and not more intensely coloured than reference solution BY_6 (*2.2.2, Method II*).

Acidity. Dissolve 1.0 g in 50 ml of *alcohol R* previously neutralised using 0.2 ml of *phenolphthalein solution R1*. Not more than 0.2 ml of *0.1 M sodium hydroxide* is required to change the colour of the indicator to pink.

Related substances. Examine by liquid chromatography (*2.2.29*) as described under Assay.

Inject 20 µl of reference solution (b). Adjust the sensitivity of the system so that the height of the peaks in the chromatogram obtained is at least 20 per cent of the full scale of the recorder. When the chromatograms are recorded in the prescribed conditions, the relative retention times are: impurity A about 0.34, impurity B about 0.36, impurity C about 0.50, impurity D about 0.65, impurity E about 0.80, impurity F about 0.85 and impurity G about 1.35. The test is not valid unless the resolution between the peaks corresponding to impurity A and impurity B is at least 1.5.

Inject 20 µl of reference solution (b) and 20 µl of the test solution. Continue the chromatography of the test solution for twice the retention time of fenofibrate. In the chromatogram obtained with the test solution, the area of any peak corresponding to impurity A, impurity B or impurity G is not greater than that of the corresponding peak in the chromatogram obtained with reference solution (b) (0.1 per cent for impurities A and B and 0.2 per cent for impurity G); the area of any peak, apart from the principal peak and any peaks corresponding to impurities A, B and G, is not greater than the area of the peak corresponding to fenofibrate in the chromatogram obtained with reference solution (b) (0.1 per cent); the sum of the areas of all the peaks, apart from the principal peak, is not greater than five times the area of the peak corresponding to fenofibrate in the chromatogram obtained with reference solution (b) (0.5 per cent). Disregard any peak with an area less than 0.1 times that of the peak due to fenofibrate in the chromatogram obtained with reference solution (b).

Halides expressed as chlorides (*2.4.4*). To 5 ml of solution S add 10 ml of *distilled water R*. The solution complies with the limit test for chlorides (100 ppm).

Sulphates (*2.4.13*). 15 ml of solution S complies with the limit test for sulphates (100 ppm).

Heavy metals (*2.4.8*). 1.0 g complies with limit test C for heavy metals (20 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 vacuo* at 60 °C.

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

ASSAY

Examine by liquid chromatography (*2.2.29*).

Test solution. Dissolve 0.100 g of the substance to be examined in the mobile phase and dilute to 100.0 ml with the mobile phase.

Reference solution (a). Dissolve 25.0 mg of *fenofibrate CRS* in the mobile phase and dilute to 25.0 ml with the mobile phase.

Reference solution (b). Dissolve 10.0 mg of *fenofibrate CRS*, 10.0 mg of *fenofibrate impurity A CRS*, 10.0 mg of *fenofibrate impurity B CRS* and 20.0 mg of *fenofibrate impurity G CRS* in the mobile phase and dilute to 100.0 ml with the mobile phase. Dilute 1.0 ml of this solution to 100.0 ml with the mobile phase.

The chromatographic procedure may be carried out using:

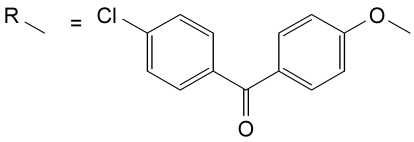
- a stainless steel column 0.25 m long and 4.0 mm in internal diameter packed with *octadecylsilyl silica gel for chromatography R* (5 µm),
- as mobile phase at a flow rate of 1 ml/min a mixture of 30 volumes of *water R* acidified to pH 2.5 with *phosphoric acid R* and 70 volumes of *acetonitrile R*,
- as detector a spectrophotometer set at 286 nm.

Inject 5 µl of reference solution (b). Adjust the sensitivity of the system so that the height of the peaks in the chromatogram is at least 50 per cent of the full scale of the recorder. Inject 5 µl of reference solution (a) six times. The assay is not valid unless the relative standard deviation of the peak area for fenofibrate is at most 1.0 per cent. Inject 5 µl of the test solution and 5 µl of reference solution (a).

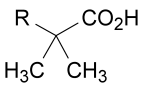
STORAGE

Store protected from light.

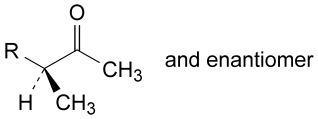
IMPURITIES



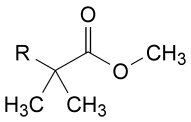
A. R-H: (4-chlorophenyl)(4-hydroxyphenyl)methanone,



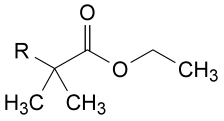
B. 2-[4-(4-chlorobenzoyl)phenoxy]-2-methylpropanoic acid (fenofibric acid),



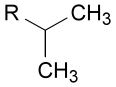
C. (3*RS*)-3-[4-(4-chlorobenzoyl)phenoxy]butan-2-one,



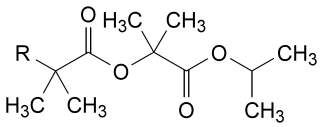
D. methyl 2-[4-(4-chlorobenzoyl)phenoxy]-2-methylpropanoate,



E. ethyl 2-[4-(4-chlorobenzoyl)phenoxy]-2-methylpropanoate,



F. (4-chlorophenyl)[4-(1-methylethoxy)phenyl]methanone,

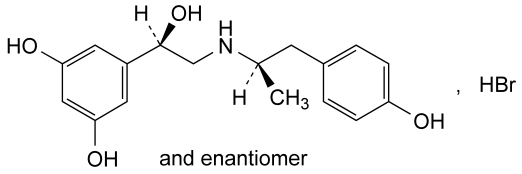


G. 1-methylethyl 2-[[2-[4-(4-chlorobenzoyl)phenoxy]-2-methylpropanoyl]oxy]-2-methylpropanoate.

01/2005:0901

FENOTEROL HYDROBROMIDE

Fenoteroli hydrobromidum



$C_{17}H_{22}BrNO_4$ M_r 384.3

DEFINITION

(1*RS*)-1-(3,5-dihydoxyphenyl)-2-[[(1*RS*)-2-(4-hydroxyphenyl)-1-methylethyl]amino]ethanol hydrobromide.

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

CHARACTERS

Appearance: white, crystalline powder.

Solubility: soluble in water and in alcohol.

IDENTIFICATION

First identification: B, E.

Second identification: A, C, D, E.

A. Dissolve 50.0 mg in *dilute hydrochloric acid R1* and dilute to 50.0 ml with the same acid. Dilute 5.0 ml to 50.0 ml with *dilute hydrochloric acid R1*. Examined between 230 nm and 350 nm (*2.2.25*), the solution shows an absorption maximum at 275 nm and a shoulder at about 280 nm. The specific absorbance at the maximum is 80 to 86.

B. Infrared absorption spectrophotometry (*2.2.24*).

Preparation: discs.

Comparison: *Ph. Eur. reference spectrum of fenoterol hydrobromide.*

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

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

Reference solution. Dissolve 10 mg of *fenoterol hydrobromide CRS* in *alcohol R* and dilute to 10 ml with the same solvent.

Plate: *TLC silica gel G plate R.*

Mobile phase: *concentrated ammonia R, water R, aldehyde-free methanol R* (1.5:10:90 *V/V/V*).

Application: 2 µl.

Development: over a path of 15 cm.

Drying: in air.

Detection: spray with a 10 g/l solution of *potassium permanganate R.*

Results: the principal spot in the chromatogram obtained with the test solution is similar in position, colour and size to the principal spot in the chromatogram obtained with the reference solution.

D. Dissolve about 10 mg in a 20 g/l solution of *disodium tetraborate R* and dilute to 50 ml with the same solution. Add 1 ml of a 10 g/l solution of *aminopyrazolone R,* 10 ml of a 2 g/l solution of *potassium ferricyanide R* and 10 ml of *methylene chloride R*. Shake and allow to separate. A reddish-brown colour develops in the lower layer.

E. It gives reaction (a) of bromides (*2.3.1*).

TESTS

Solution S. Dissolve 2.00 g in *carbon dioxide-free water R* and dilute to 50.0 ml with the same solvent.

Appearance of solution. Solution S is clear (*2.2.1*) and not more intensely coloured than reference solution Y_7 (*2.2.2, Method II*).

pH (*2.2.3*): 4.2 to 5.2 for solution S.

Phenone: maximum 0.2 per cent. The absorbance (*2.2.25*) of solution S at 330 nm has a maximum of 0.42.

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

Test solution. Dissolve 25.0 mg of the substance to be examined in *water R* and dilute to 10.0 ml with the same solvent.

Reference solution. Dissolve 25.0 mg of *fenoterol hydrobromide CRS* in *water R* and dilute to 10.0 ml with the same solvent.

Column:

– *size*: *l* = 0.25 m, Ø = 4.6 mm,

– *stationary phase*: *octadecylsilyl silica gel for chromatography R* (5 µm to 10 µm).

Mobile phase: to a mixture of 1 volume of a 9 g/l solution of *potassium dihydrogen phosphate R* and 69 volumes of a 24 g/l solution of *disodium hydrogen phosphate R,* adjusted to pH 8.5 using *phosphoric acid R,* add 30 volumes of *methanol R.*

Flow rate: 1 ml/min.

Detection: spectrophotometer at 280 nm.

Injection: 20 µl loop injector.

Sensitivity: the height of the peak due to the diastereoisomers eluting immediately after the principal peak is not less than 10 per cent of the full scale of the recorder.

System suitability: reference solution:

– the height of the trough separating the peak due to the diastereoisomers from the principal peak is less than 4 per cent of the full scale of the recorder,

– the retention time of the principal peak is less than 20 min.

Limits:

Calculate the content of diastereoisomers by determining the height of a perpendicular dropped from the apex of the peak to a line drawn from the trough between the 2 peaks to the baseline, and taking into account the declared content of diastereoisomers in *fenoterol hydrobromide CRS* (4.0 per cent).

Iron (*2.4.9*): maximum 5 ppm.

Dissolve the residue from the test for sulphated ash in 2.5 ml of *dilute hydrochloric acid R* and dilute to 10 ml with *water R*. The solution complies with the limit test for iron.

Loss on drying (*2.2.32*): maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 100-105 °C.

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