Reference solution (a). Dissolve 2 mg of *flutamide CRS* and 2 mg of *flutamide impurity C CRS* in the mobile phase, then dilute to 50.0 ml with the mobile phase. Dilute 1.0 ml of this solution to 20.0 ml with the mobile phase.

Reference solution (b). Dilute 1.0 ml of the test solution to 50.0 ml with the mobile phase. Dilute 2.0 ml of this solution to 20.0 ml with the mobile phase.

Column:

– *size*: *l* = 0.25 m, Ø = 4.0 mm;

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

Mobile phase: *acetonitrile R, water R* (50:50 *V/V*).

Flow rate: 0.5 ml/min.

Detection: spectrophotometer at 240 nm.

Injection: 20 µl.

Run time: 1.5 times the retention time of flutamide.

Retention time: impurity C = about 14 min; flutamide = about 19 min.

Relative retention with reference to flutamide: impurity C = about 0.72.

System suitability: reference solution (a):

– *resolution*: minimum 10.5 between the peaks due to impurity C and flutamide.

Limits:

– *impurity C*: not more than 1.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.3 per cent);

– *impurities A, B, D, E, F*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.2 per cent);

– *total*: not more than 2.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.5 per cent);

– *disregard limit*: 0.25 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent).

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

1.0 g complies with test C. Prepare the reference solution using 2 ml of *lead standard solution (10 ppm Pb) R*.

Loss on drying (*2.2.32*): maximum 0.5 per cent, determined on 1.000 g by drying *in vacuo* at 60 °C for 3 h.

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

ASSAY

Dissolve 25.0 mg in *methanol R* and dilute to 25.0 ml with the same solvent. Dilute 2.0 ml of this solution to 100.0 ml with *methanol R*. Measure the absorbance (*2.2.25*) at the absorption maximum at 295 nm.

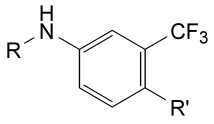
Calculate the content of $C_{11}H_{11}F_3N_2O_3$ taking the specific absorbance to be 295.

STORAGE

Protected from light.

IMPURITIES

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

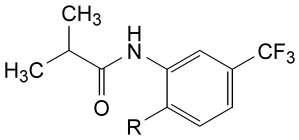


A. R = H, R′ = NO_2: 4-nitro-3-(trifluoromethyl)aniline,

B. R = CO-CH_3, R′ = NO_2: *N*-[4-nitro-3-(trifluoromethyl)-phenyl]acetamide,

C. R = CO-CH_2-CH_3, R′ = NO_2: *N*-[4-nitro-3-(trifluoromethyl)phenyl]propanamide,

D. R = R′ = H: 3-(trifluoromethyl)aniline,



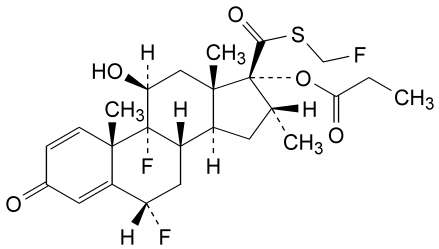
E. R = H: 2-methyl-*N*-[3-(trifluoromethyl)phenyl]propanamide,

F. R = NO_2: 2-methyl-*N*-[2-nitro-5-(trifluoromethyl)-phenyl]propanamide.

01/2008:1750

FLUTICASONE PROPIONATE

Fluticasoni propionas



$C_{25}H_{31}F_3O_5S$ M_r 500.6

[80474-14-2]

DEFINITION

6α,9-Difluoro-17-[[(fluoromethyl)sulphanyl]carbonyl]-11β-hydroxy-16α-methyl-3-oxoandrosta-1,4-dien-17α-yl propanoate.

Content: 97.0 per cent to 102.0 per cent (anhydrous substance).

CHARACTERS

Appearance: white or almost white powder.

Solubility: practically insoluble in water, sparingly soluble in methylene chloride, slightly soluble in alcohol.

IDENTIFICATION

A. Infrared absorption spectrophotometry (*2.2.24*).
Comparison: *fluticasone propionate CRS*.

B. Examine the chromatograms obtained in the assay.
Results: the principal peak in the chromatogram obtained with the test solution is similar in retention time to the principal peak in the chromatogram obtained with reference solution (b).

TESTS

Specific optical rotation (*2.2.7*): + 32 to + 36 (anhydrous substance).

Dissolve 0.25 g in *methylene chloride R* and dilute to 50.0 ml with the same solvent.

Related substances. Liquid chromatography (*2.2.29*): use the normalisation procedure.

Test solution. Dissolve 20 mg of the substance to be examined in a mixture of equal volumes of mobile phase A and mobile phase B and dilute to 100.0 ml with the same mixture of mobile phases.

Reference solution (a). Dissolve 4 mg of *fluticasone impurity D CRS* in a mixture of equal volumes of mobile phase A and mobile phase B and dilute to 100.0 ml with the same mixture of mobile phases.

Reference solution (b). Dissolve 20 mg of *fluticasone propionate CRS* in a mixture of equal volumes of mobile phase A and mobile phase B, add 1.0 ml of reference solution (a) and dilute to 100.0 ml with a mixture of equal volumes of mobile phase A and mobile phase B.

Column:

– *size*: *l* = 0.25 m, Ø = 4.6 mm,
– *stationary phase*: *octadecylsilyl silica gel for chromatography R* (5 µm),
– *temperature*: 40 °C.

Mobile phase:

– *mobile phase A*: a solution containing 0.05 per cent *V/V* of *phosphoric acid R* and 3.0 per cent *V/V* of *methanol R* in *acetonitrile R*,
– *mobile phase B*: a solution containing 0.05 per cent *V/V* of *phosphoric acid R* and 3.0 per cent *V/V* of *methanol R* in *water R*,

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 40	43 → 55	57 → 45
40 - 60	55 → 90	45 → 10
60 - 70	90	10
70 - 75	90 → 43	10 → 57

Flow rate: 1 ml/min.

Detection: spectrophotometer at 239 nm.

Injection: 50 µl; inject the test solution and reference solution (b).

Relative retention with reference to fluticasone propionate (retention time = about 30 min): impurity A = about 0.38; impurity B = about 0.46; impurity C = about 0.76; impurity D = about 0.95; impurity E = about 1.12; impurity F = about 1.18; impurity G = about 1.33; impurity H = about 1.93; impurity I = about 2.01.

System suitability: reference solution (b):

– *resolution*: minimum 1.5 between the peaks due to impurity D and to fluticasone propionate.

Limits:

– *impurities D, G*: for each impurity, maximum 0.3 per cent,
– *impurities A, B, C, E, F, H, I*: for each impurity, maximum 0.2 per cent,
– *impurity with relative retention at about 1.23*: maximum 0.2 per cent,
– *any other impurity*: maximum 0.1 per cent,
– *total*: maximum 1.2 per cent,
– *disregard limit*: 0.05 per cent.

Acetone. Gas chromatography (*2.2.28*).

Internal standard solution. Dilute 0.5 ml of *tetrahydrofuran R* to 1000 ml with *dimethylformamide R*.

Test solution. Dissolve 0.50 g of the substance to be examined in the internal standard solution and dilute to 10.0 ml with the same solution.

Reference solution. Dilute 0.40 g of *acetone R* to 100.0 ml with the internal standard solution. Dilute 1.0 ml to 10.0 ml with the internal standard solution.

Column:

– *material*: fused silica,
– *size*: *l* = 25 m, Ø = 0.53 mm,
– *stationary phase*: cross-linked *macrogol 20 000 R* (film thickness 2 µm).

Carrier gas: *nitrogen for chromatography R*.

Flow rate: 5.5 ml/min.

Temperature:

	Time (min)	Temperature (°C)
Column	0 - 3.5	60
	3.5 - 7.5	60 → 180
	7.5 - 10.5	180
Injection port		150
Detector		250

Detection: flame ionisation.

Injection: 0.1 µl.

Limit:

– *acetone*: maximum 1.0 per cent *m/m*.

Water (*2.5.12*): maximum 0.5 per cent determined on 0.250 g.

Use as solvent a mixture of equal volumes of *chloroform R* and *methanol R*.

ASSAY

Liquid chromatography (*2.2.29*).

Test solution. Dissolve 20.0 mg of the substance to be examined in the mobile phase and dilute to 50.0 ml with the mobile phase. Dilute 1.0 ml to 10.0 ml with the mobile phase.

Reference solution (a). Dissolve 20.0 mg of *fluticasone propionate CRS* in the mobile phase and dilute to 50.0 ml with the mobile phase.

Reference solution (b). Dilute 1.0 ml of reference solution (a) to 10.0 ml with the mobile phase.

Reference solution (c). Dissolve 4.0 mg of *fluticasone impurity D CRS* in the mobile phase and dilute to 50.0 ml with the mobile phase. To 1.0 ml of this solution, add 1.0 ml of reference solution (a) and dilute to 10.0 ml with the mobile phase.

Column:

– *size*: *l* = 0.25 m, Ø = 4.6 mm,
– *stationary phase*: *octadecylsilyl silica gel for chromatography R* (5 µm),
– *temperature*: 40 °C.

Mobile phase: mix 15 volumes of *acetonitrile R*, 35 volumes of a 1.15 g/l solution of *ammonium dihydrogen phosphate R* adjusted to pH 3.5 and 50 volumes of *methanol R*.

Flow rate: 1.5 ml/min.

Detection: spectrophotometer at 239 nm.

Injection: 20 µl; inject the test solution and reference solutions (b) and (c).

System suitability: reference solution (c):

– *resolution*: minimum 1.5 between the peaks due to impurity D and to fluticasone propionate.

If necessary, adjust the ratio of acetonitrile to methanol in the mobile phase.

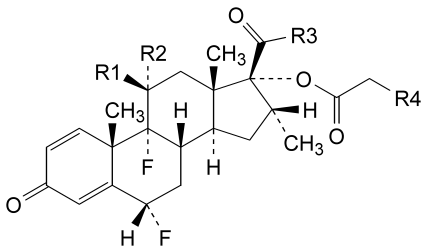
Calculate the percentage content of $C_{25}H_{31}F_3O_5S$ using the chromatograms obtained with the test solution and reference solution (b), and the declared content of *fluticasone propionate CRS*.

STORAGE

Protected from light.

IMPURITIES

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



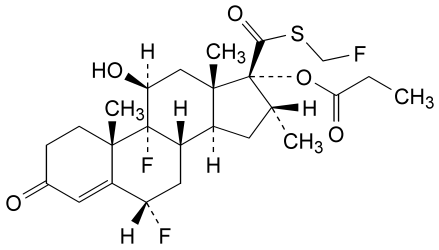
A. R1 = R3 = OH, R2 = H, R4 = CH_3: 6α,9-difluoro-11β-hydroxy-16α-methyl-3-oxo-17-(propanoyloxy)androsta-1,4-diene-17β-carboxylic acid,

B. R1 = OH, R2 = H, R3 = S-OH, R4 = CH_3: [[6α,9-difluoro-11β-hydroxy-16α-methyl-3-oxo-17-(propanoyloxy)androsta-1,4-dien-17β-yl]carbonyl]sulphenic acid,

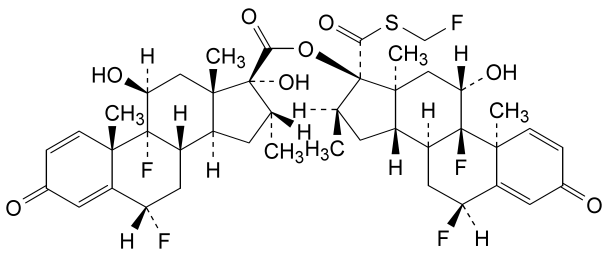
C. R1 = OH, R2 = R4 = H, R3 = S-CH_2-F: 6α,9-difluoro-17-[[(fluoromethyl)sulphanyl]carbonyl]-11β-hydroxy-16α-methyl-3-oxoandrosta-1,4-dien-17α-yl acetate,

D. R1 = OH, R2 = H, R3 = S-CH_3, R4 = CH_3: 6α,9-difluoro-17-[(methylsulphanyl)carbonyl]-11β-hydroxy-16α-methyl-3-oxoandrosta-1,4-dien-17α-yl propanoate,

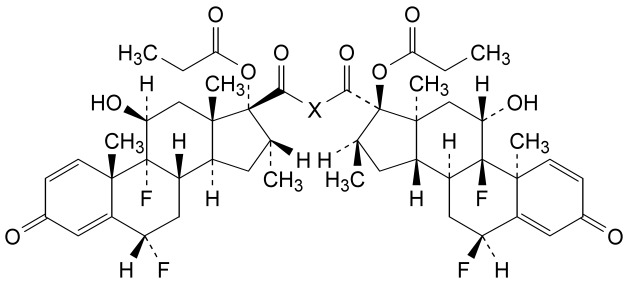
F. R1 + R2 = O, R3 = S-CH_2-F, R4 = CH_3: 6α,9-difluoro-17-[[(fluoromethyl)sulphanyl]carbonyl]-16α-methyl-3,11-dioxoandrosta-1,4-dien-17α-yl propanoate,



E. 6α,9-difluoro-17-[[(fluoromethyl)sulphanyl]carbonyl]-11β-hydroxy-16α-methyl-3-oxoandrost-4-en-17α-yl propanoate,



G. 6α,9-difluoro-17-[[(fluoromethyl)sulphanyl]carbonyl]-11β-hydroxy-16α-methyl-3-oxoandrosta-1,4-dien-17α-yl 6α,9-difluoro-11β,17-dihydroxy-16α-methyl-3-oxoandrosta-1,4-diene-17β-carboxylate,



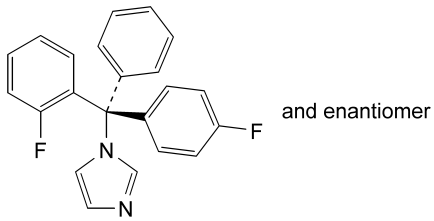
H. X = S-S: 17,17′-(disulphanediyldicarbonyl)bis(6α,9-difluoro-11β-hydroxy-16α-methyl-3-oxoandrosta-1,4-dien-17α-yl) dipropanoate,

I. X = S-S-S: 17,17′-(trisulphanediyldicarbonyl)bis(6α,9-difluoro-11β-hydroxy-16α-methyl-3-oxoandrosta-1,4-dien-17α-yl) dipropanoate.

01/2008:1424
corrected 6.0

FLUTRIMAZOLE

Flutrimazolum



$C_{22}H_{16}F_2N_2$ M_r 346.4
[119006-77-8]

DEFINITION

(*RS*)-1-[(2-Fluorophenyl)(4-fluorophenyl)phenylmethyl]-1*H*-imidazole.

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

CHARACTERS

Appearance: white or almost white powder.

Solubility: practically insoluble in water, freely soluble in tetrahydrofuran, soluble in methanol.

IDENTIFICATION

First identification: B.

Second identification: A, C, D.

A. Melting point (*2.2.14*): 161 °C to 166 °C.

B. Infrared absorption spectrophotometry (*2.2.24*).

Preparation: discs.

Comparison: *flutrimazole CRS.*

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

Test solution. Dissolve 20 mg of the substance to be examined in *acetone R* and dilute to 10 ml with the same solvent.

Reference solution (a). Dissolve 20 mg of *flutrimazole CRS* in *acetone R* and dilute to 10 ml with the same solvent.