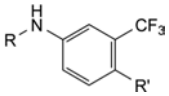
Calculate the content of $C_{11}H_{11}F_3N_2O_3$ taking the specific absorbance to be 295.

STORAGE

Protected from light.

IMPURITIES

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

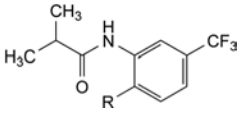


A. R = H, R′ = $NO_2$: 4-nitro-3-(trifluoromethyl)aniline,

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,



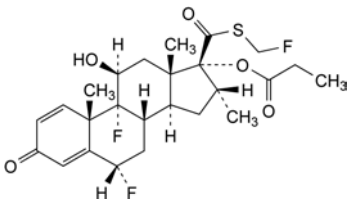
E. R = H: 2-methyl-*N*-[3-(trifluoromethyl)phenyl]propanamide,

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)sulfanyl]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.

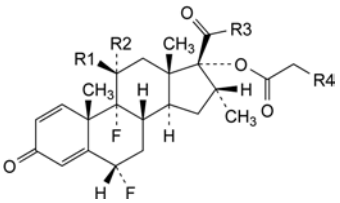
Calculate the percentage content of $C_{25}H_{31}F_3O_5S$ using the chromatograms obtained with the test solution and reference solution (b), and the declared content of *fluticasone propionate CRS*.

STORAGE

Protected from light.

IMPURITIES

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



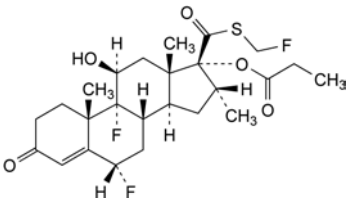
A. R1 = R3 = OH, R2 = H, R4 = $CH_3$: 6α,9-difluoro-11β-hydroxy-16α-methyl-3-oxo-17-(propanoyloxy)androsta-1,4-diene-17β-carboxylic acid,

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]sulfenic acid,

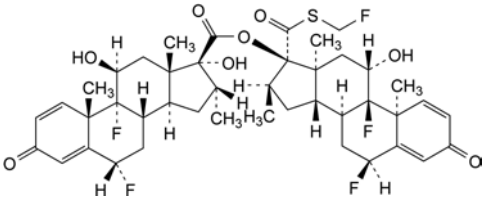
C. R1 = OH, R2 = R4 = H, R3 = S-$CH_2$-F: 6α,9-difluoro-17-[[(fluoromethyl)sulfanyl]carbonyl]-11β-hydroxy-16α-methyl-3-oxoandrosta-1,4-dien-17α-yl acetate,

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

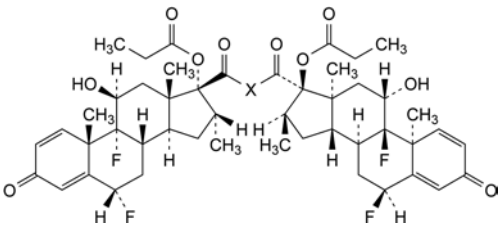
F. R1 + R2 = O, R3 = S-$CH_2$-F, R4 = $CH_3$: 6α,9-difluoro-17-[[(fluoromethyl)sulfanyl]carbonyl]-16α-methyl-3,11-dioxoandrosta-1,4-dien-17α-yl propanoate,



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



G. 6α,9-difluoro-17-[[(fluoromethyl)sulfanyl]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′-(disulfanediyldicarbonyl)bis(6α,9-difluoro-11β-hydroxy-16α-methyl-3-oxoandrosta-1,4-dien-17α-yl) dipropanoate,

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