UNIVERSITÀ DEGLI STUDI DI TORINO

ESAME DI STATO PER L'ABILITAZIONE ALL'ESERCIZIO DELLA PROFESSIONE DI FARMACISTA

SECONDA SESSIONE 2018

PROVA SCRITTA

Tema n. 1
Preparazioni galeniche contenenti *Cannabis*: modalità prescrittive, formalismi del Medico e obblighi del Farmacista.

Tema n. 2
Preparazioni oftalmiche: il consiglio del Farmacista per il corretto utilizzo e aderenza alla terapia.

Tema n. 3
I macrolidi: effetti, indicazioni e controindicazioni.

PROVA PRATICA

Prova n.1
Riconoscimento del farmaco.
Vedi allegato di seguito.

Prova n.2
Dosamento del farmaco.
Vedi allegato di seguito.

Prova n.3
Spedizione della ricetta.
Vedi allegato di seguito.

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SECONDA SESSIONE 2018

PROVA PRATICA: Prova di riconoscimento del farmaco

Cognome e nome.....

La prova consiste nel ***riconoscimento di due farmaci.***

Per ogni farmaco viene fornito il profilo sperimentale (sequenza delle analisi effettuate) ed una indicazione di possibili farmaci candidati corredati dalle rispettive monografie provenienti dalla Farmacopea Europea (Eur. Ph. 9).

Al candidato viene richiesto di:

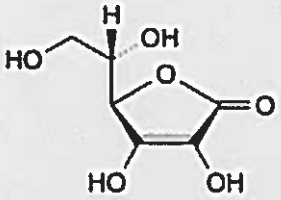
- individuare il farmaco che meglio corrisponde al profilo fornito;
- motivare brevemente la propria scelta;
- proporre ulteriori prove sperimentali a conferma della scelta effettuata.

Riconoscimento del farmaco: *primo riconoscimento*

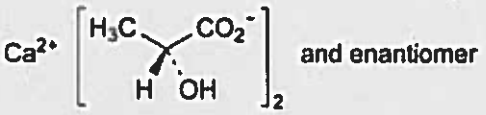
Il farmaco in esame si presenta come polvere cristallina piuttosto bianca, molto solubile in acqua e moderatamente solubile in etanolo.

Se ad una soluzione acquosa del farmaco si aggiungono alcune gocce di una soluzione di $KMnO_4$ si osserva decolorazione.

In base a queste caratteristiche sono stati individuati tra i farmaci presenti in Farmacopea Europea 2 possibili candidati: ACIDO ASCORBICO e CALCIO LATTATO.



ACIDO ASCORBICO



CALCIO LATTATO

2,5 g di polvere sono stati solubilizzati in 25,00 mL di acqua; la soluzione così ottenuta è stata utilizzata per misurare il potere rotatorio specifico, ottenendo +20,5.

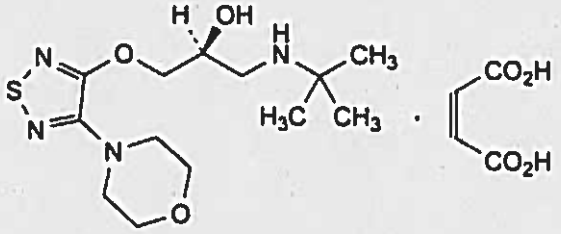
Indicare a quale dei due farmaci corrisponde il profilo sperimentale fornito motivando tale scelta e proporre ulteriori prove sperimentali per validare la scelta effettuata.

Riconoscimento del farmaco: *secondo riconoscimento*

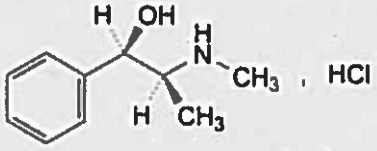
Il farmaco in esame si presenta come una polvere bianca cristallina, solubile in acqua ed etanolo.

Se ad una soluzione del farmaco si aggiungono alcune gocce di una soluzione di $CuSO_4$ e di una soluzione concentrata di NaOH, si sviluppa una colorazione viola; in seguito ad estrazione con cloruro di metilene la fase organica inferiore è di colore grigio scuro, mentre la fase acquosa superiore diventa blu.

In base alle caratteristiche sopra riportate sono stati individuati tra i farmaci presenti in Farmacopea Europea 2 possibili candidati: TIMOLOLO MALEATO ed EFEDRINA CLORIDRATO.



TIMOLOLO MALEATO

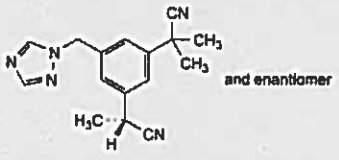


EFEDRINA CLORIDRATO

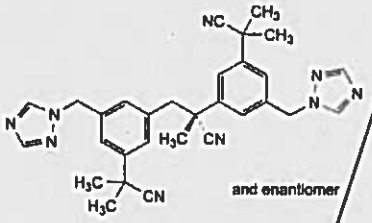
Indicare a quale dei due farmaci corrisponde il profilo sperimentale fornito, sapendo che la sostanza fonde intorno a 219°C senza decomposizione. Motivare la scelta effettuata e proporre ulteriori prove sperimentali per validarla.

IMPURITIES

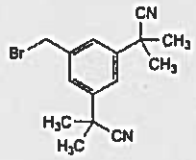
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph *Substances for pharmaceutical 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*): *A, B, C, D, E, F, G, H, I.*



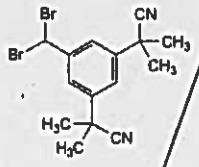
A. 2-[3-[(1*RS*)-1-cyanoethyl]-5-(1*H*-1,2,4-triazol-1-ylmethyl)phenyl]-2-methylpropanenitrile,



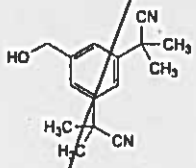
B. (2*RS*)-2,3-bis[3-(1-cyano-1-methylethyl)-5-(1*H*-1,2,4-triazol-1-ylmethyl)phenyl]-2-methylpropanenitrile,



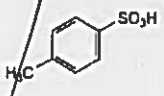
C. 2,2′-[5-(bromomethyl)benzene-1,3-diyl]bis(2-methylpropanenitrile),



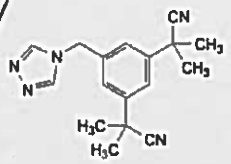
D. 2,2′-[5-(dibromomethyl)benzene-1,3-diyl]bis(2-methylpropanenitrile),



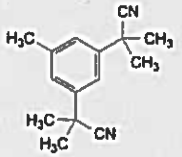
E. 2,2′-[5-(hydroxymethyl)benzene-1,3-diyl]bis(2-methylpropanenitrile),



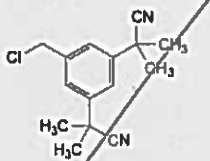
F. 4-methylbenzenesulfonic acid,



G. 2,2′-[5-(4*H*-1,2,4-triazol-4-ylmethyl)benzene-1,3-diyl]bis(2-methylpropanenitrile),



H. 2,2′-(5-methylbenzene-1,3-diyl)bis(2-methylpropanenitrile),



I. 2,2′-[5-(chloromethyl)benzene-1,3-diyl]bis(2-methylpropanenitrile).

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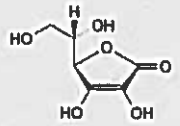
corrected 9.3

ASCORBIC ACID

Acidum ascorbicum



$C_6H_8O_6$ M_r 176.1
[50-81-7]

DEFINITION

(5*R*)-5-[(1*S*)-1,2-Dihydroxyethyl]-3,4-dihydroxyfuran-2(5*H*)-one.

Content: 99.0 per cent to 100.5 per cent.

CHARACTERS

Appearance: white or almost white, crystalline powder or colourless crystals, becoming discoloured on exposure to air and moisture.

Solubility: freely soluble in water, sparingly soluble in ethanol (96 per cent).

mp: about 190 °C, with decomposition.

IDENTIFICATION

First identification: B, C.

Second identification: A, C, D.

A. Ultraviolet and visible absorption spectrophotometry (*2.2.25*).

Test solution. Dissolve 0.10 g in *water R* and dilute immediately to 100.0 mL with the same solvent. Add 1.0 mL of the solution to 10 mL of a 10.3 g/L solution of *hydrochloric acid R* and dilute to 100.0 mL with *water R*.

Monographs A-C

Absorption maximum: at 243 nm, determined immediately after dissolution.

Specific absorbance at the absorption maximum: 545 to 585.

B. Infrared absorption spectrophotometry (2.2.24).

Comparison: *ascorbic acid CRS*.

C. pH (2.2.3): 2.1 to 2.6 for solution S (see Tests).

D. To 1 mL of solution S add 0.2 mL of *dilute nitric acid R* and 0.2 mL of *silver nitrate solution R2*. A grey precipitate is formed.

TESTS

Solution S. Dissolve 1.0 g in *carbon dioxide-free water R* and dilute to 20 mL with the same solvent.

Appearance of solution. Solution S is clear (2.2.1) and not more intensely coloured than reference solution BY_7 (2.2.2, *Method II*).

Specific optical rotation (2.2.7): + 20.5 to + 21.5.

Dissolve 2.50 g in *water R* and dilute to 25.0 mL with the same solvent.

Impurity E: maximum 0.3 per cent.

Test solution. Dissolve 0.25 g in 5 mL of *water R*. Neutralise using *dilute sodium hydroxide solution R*, then add 1 mL of *dilute acetic acid R* and 0.5 mL of *calcium chloride solution R*.

Reference solution. Dissolve 70 mg of *oxalic acid R* in *water R* and dilute to 500 mL with the same solvent; to 5 mL of the solution add 1 mL of *dilute acetic acid R* and 0.5 mL of *calcium chloride solution R*.

Allow the solutions to stand for 1 h. Any opalescence in the test solution is not more intense than that in the reference solution.

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

Phosphate buffer solution. Dissolve 6.8 g of *potassium dihydrogen phosphate R* in *water R* and dilute to about 175 mL with the same solvent. Filter through a membrane filter (nominal pore size 0.45 µm) and dilute to 1000 mL with *water R*.

Test solution. Dissolve 0.500 g of the substance to be examined in the mobile phase and dilute to 10.0 mL with the mobile phase.

Reference solution (a). Dissolve 10.0 mg of *ascorbic acid impurity C CRS* in the mobile phase and dilute to 5.0 mL with the mobile phase.

Reference solution (b). Dissolve 5.0 mg of *ascorbic acid impurity D CRS* and 5.0 mg of *ascorbic acid CRS* in the mobile phase, add 2.5 mL of reference solution (a) and dilute to 100.0 mL with the mobile phase.

Reference solution (c). Dilute 1.0 mL of the test solution to 200.0 mL with the mobile phase. Mix 1.0 mL of this solution with 1.0 mL of reference solution (a).

Column:

- *size*: *l* = 0.25 m, Ø = 4.6 mm;
- *stationary phase*: *aminopropylsilyl silica gel for chromatography R* (5 µm);
- *temperature*: 45 °C.

Mobile phase: phosphate buffer solution, *acetonitrile R1* (25:75 *V/V*).

Flow rate: 1.0 mL/min.

Detection: spectrophotometer at 210 nm.

Injection: 20 µL of the test solution and reference solutions (b) and (c).

Run time: 2.5 times the retention time of ascorbic acid.

Identification of impurities: use the chromatogram obtained with reference solution (b) to identify the peaks due to impurities C and D.

Relative retention with reference to ascorbic acid (retention time = about 11 min): impurity D = about 0.4; impurity C = about 1.7.

System suitability:

- *resolution*: minimum 3.0 between the peaks due to ascorbic acid and impurity C in the chromatogram obtained with reference solution (c);
- *signal-to-noise ratio*: minimum 20 for the peak due to impurity C in the chromatogram obtained with reference solution (b).

Limits:

- *impurities C, D*: for each impurity, not more than 1.5 times the area of the corresponding peak in the chromatogram obtained with reference solution (b) (0.15 per cent);
- *unspecified impurities*: for each impurity, not more than the area of the peak due to ascorbic acid in the chromatogram obtained with reference solution (b) (0.10 per cent);
- *sum of impurities other than C and D*: not more than twice the area of the peak due to ascorbic acid in the chromatogram obtained with reference solution (b) (0.2 per cent);
- *disregard limit*: 0.5 times the area of the peak due to ascorbic acid in the chromatogram obtained with reference solution (b) (0.05 per cent).

Copper: maximum 5 ppm.

Atomic absorption spectrometry (2.2.23, *Method I*).

Test solution. Dissolve 2.0 g in *0.1 M nitric acid* and dilute to 25.0 mL with the same acid.

Reference solutions. Prepare the reference solutions (0.2 ppm, 0.4 ppm and 0.6 ppm) using *copper standard solution (10 ppm Cu) R*, diluting with *0.1 M nitric acid*.

Source: copper hollow-cathode lamp.

Wavelength: 324.8 nm.

Atomisation device: air-acetylene flame.

Adjust the zero of the apparatus using *0.1 M nitric acid*.

Iron: maximum 2 ppm.

Atomic absorption spectrometry (2.2.23, *Method I*).

Test solution. Dissolve 5.0 g in *0.1 M nitric acid* and dilute to 25.0 mL with the same acid.

Reference solutions. Prepare the reference solutions (0.2 ppm, 0.4 ppm and 0.6 ppm) using *iron standard solution (20 ppm Fe) R*, diluting with *0.1 M nitric acid*.

Source: iron hollow-cathode lamp.

Wavelength: 248.3 nm.

Atomisation device: air-acetylene flame.

Adjust the zero of the apparatus using *0.1 M nitric acid*.

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

ASSAY

Dissolve 0.150 g in a mixture of 10 mL of *dilute sulfuric acid R* and 80 mL of *carbon dioxide-free water R*. Add 1 mL of *starch solution R*. Titrate with *0.05 M iodine* until a persistent violet-blue colour is obtained.

1 mL of *0.05 M iodine* is equivalent to 8.81 mg of $C_6H_8O_6$.

STORAGE

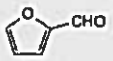
In a non-metallic container, protected from light.

IMPURITIES

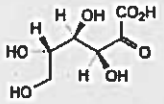
Specified impurities: C, D, E.

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*

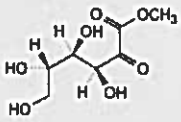
(2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also *5.10. Control of impurities in substances for pharmaceutical use*): *A, F, G, H.*



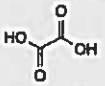
A. 2-furaldehyde,



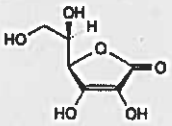
C. L-*xylo*-hex-2-ulosonic acid (L-sorbosonic acid),



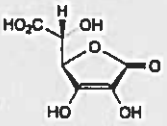
D. methyl L-*xylo*-hex-2-ulosonate (methyl L-sorbosonate),



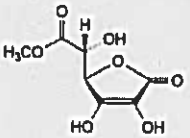
E. oxalic acid,



F. (5*R*)-5-[(1*R*)-1,2-dihydroxyethyl]-3,4-dihydroxyfuran-2(5*H*)-one,



G. (2*R*)-2-[(2*R*)-3,4-dihydroxy-5-oxo-2,5-dihydrofuran-2-yl]-2-hydroxyacetic acid,

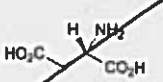


H. methyl (2*R*)-2-[(2*R*)-3,4-dihydroxy-5-oxo-2,5-dihydrofuran-2-yl]-2-hydroxyacetate.

01/2018:0797

ASPARTIC ACID

Acidum asparticum



$C_4H_7NO_4$ M_r 133.1

[56-84-8]

DEFINITION

(2*S*)-2-Aminobutanedioic acid (L-aspartic acid).

Content: 98.5 per cent to 101.5 per cent (dried substance).

CHARACTERS

Appearance: white or almost white, crystalline powder or colourless crystals.

Solubility: slightly soluble in water, practically insoluble in ethanol (96 per cent). It dissolves in dilute mineral acids and in dilute solutions of alkali hydroxides.

IDENTIFICATION

First identification: *carry out either tests A, C or tests C, D.*

Second identification: *A, B, E.*

A. Specific optical rotation (*2.2.7*): + 24.0 to + 26.0 (dried substance).

Dissolve 2.00 g in *hydrochloric acid R1* and dilute to 25.0 mL with the same acid.

B. A suspension of 1 g in 10 mL of *water R* is strongly acid (*2.2.4*).

C. Infrared absorption spectrophotometry (*2.2.24*).

Comparison: *aspartic acid CRS.*

D. Enantiomeric purity (see Tests).

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

Test solution. Dissolve 10 mg of the substance to be examined in 2 mL of *dilute ammonia R1* and dilute to 50 mL with *water R.*

Reference solution. Dissolve 10 mg of *aspartic acid CRS* in 2 mL of *dilute ammonia R1* and dilute to 50 mL with *water R.*

Plate: *TLC silica gel plate R.*

Mobile phase: *glacial acetic acid R, water R, butanol R* (20:20:60 *V/V/V*).

Application: 5 µL.

Development: over 2/3 of the plate.

Drying: in air.

Detection: spray with *ninhydrin solution R* and heat at 105 °C for 15 min.

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.

TESTS

Appearance of solution. The solution is clear (*2.2.1*) and not more intensely coloured than reference solution BY_6 (*2.2.2, Method II*).

Dissolve 0.5 g in a 103 g/L solution of *hydrochloric acid R* and dilute to 10 mL with the same acid.

Enantiomeric purity. Liquid chromatography (*2.2.29*).

Test solution. Dissolve 0.100 g of the substance to be examined in *water R* and dilute to 100.0 mL with the same solvent.

Reference solution (a). Dissolve 0.100 g of D-*aspartic acid R* (impurity I) in *water R* and dilute to 100.0 mL with the same solvent.

Reference solution (b). Dissolve 0.100 g of the substance to be examined in 90 mL of *water R*, add 0.3 mL of reference solution (a) and dilute to 100.0 mL with *water R.*

Reference solution (c). Dilute 0.3 mL of reference solution (a) to 100.0 mL with *water R.*

Column:

- *size*: *l* = 0.15 m, Ø = 4.6 mm;
- *stationary phase*: *L-penicillamine coated silica gel for chiral separations R* (5 µm);
- *temperature*: 30 °C.

Mobile phase: *2-propanol R*, 0.5 g/L solution of *copper sulfate pentahydrate R* (5:95 *V/V*).

Flow rate: 1.0 mL/min.

Detection: spectrophotometer at 230 nm.

ASSAY

Dissolve 0.4 g in 12 mL of *dilute hydrochloric acid R* by heating on a water bath if necessary and dilute to 200 mL with *water R*. To 20.0 mL of this solution add 25.0 mL of *0.02 M sodium edetate*, 50 mL of *water R*, 5 mL of *ammonium chloride buffer solution pH 10.7 R* and about 25 mg of *mordant black 11 triturate R*. Titrate the excess of sodium edetate with *0.02 M zinc sulfate*. Carry out a blank titration.

1 mL of *0.02 M sodium edetate* is equivalent to 3.44 mg of $CaHPO_4,2H_2O$.

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). Some of the characteristics described in the Functionality-related characteristics section may also be present in the mandatory part of the monograph since they also represent mandatory quality criteria. In such cases, a cross-reference to the tests described in the mandatory part is included in the Functionality-related characteristics section. Control of the characteristics can 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 calcium hydrogen phosphate dihydrate used as filler in tablets and capsules.

Particle-size distribution (*2.9.31* or *2.9.38*).

Bulk and tapped density (*2.9.34*).

Powder flow (*2.9.36*).

01/2017:1078

CALCIUM HYDROXIDE

Calcii hydroxidum

$Ca(OH)_2$ M_r 74.1

[1305-62-0]

DEFINITION

Content: 95.0 per cent to 100.5 per cent.

CHARACTERS

Appearance: white or almost white, fine powder.

Solubility: practically insoluble in water.

IDENTIFICATION

A. To 0.80 g in a mortar, add 10 mL of *water R* and 0.5 mL of *phenolphthalein solution R* and mix. The suspension turns red. On addition of 17.5 mL of *1 M hydrochloric acid*, the suspension becomes colourless without effervescing. The red colour occurs again when the mixture is triturated for 1 min. On addition of a further 6 mL of *1 M hydrochloric acid* and triturating, the solution becomes colourless.

B. Dissolve about 0.1 g in *dilute hydrochloric acid R* and dilute to 10 mL with *water R*. 5 mL of the solution give reaction (b) of calcium (*2.3.1*).

TESTS

Matter insoluble in hydrochloric acid: maximum 0.5 per cent.

Dissolve 2.0 g in 30 mL of *hydrochloric acid R*. Boil the solution and filter. Wash the residue with hot *water R*. The residue weighs a maximum of 10 mg.

Carbonates: maximum 5.0 per cent of $CaCO_3$.

Add 5.0 mL of *1 M hydrochloric acid* to the titrated solution obtained under Assay and titrate with *1 M sodium hydroxide* using 0.5 mL of *methyl orange solution R* as indicator.

1 mL of *1 M hydrochloric acid* is equivalent to 50.05 mg of $CaCO_3$.

Chlorides (*2.4.4*): maximum 330 ppm.

Dissolve 0.30 g in a mixture of 2 mL of *nitric acid R* and 10 mL of *water R* and dilute to 30 mL with *water R*.

Sulfates (*2.4.13*): maximum 0.4 per cent.

Dissolve 0.15 g in a mixture of 5 mL of *dilute hydrochloric acid R* and 10 mL of *distilled water R* and dilute to 60 mL with *distilled water R*.

Arsenic (*2.4.2, Method A*): maximum 4 ppm.

Dissolve 0.50 g in 5 mL of *brominated hydrochloric acid R* and dilute to 50 mL with *water R*. Use 25 mL of this solution.

Magnesium and alkali metals: maximum 4.0 per cent calculated as sulfates.

Dissolve 1.0 g in a mixture of 10 mL of *hydrochloric acid R* and 40 mL of *water R*. Boil and add 50 mL of a 63 g/L solution of *oxalic acid R*. Neutralise with *ammonia R* and dilute to 200 mL with *water R*. Allow to stand for 1 h and filter through a suitable filter. To 100 mL of the filtrate, add 0.5 mL of *sulfuric acid R*. Cautiously evaporate to dryness and ignite. The residue weighs a maximum of 20 mg.

ASSAY

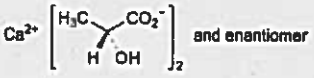
To 1.500 g in a mortar, add 20-30 mL of *water R* and 0.5 mL of *phenolphthalein solution R*. Titrate with *1 M hydrochloric acid* by triturating the substance until the red colour disappears. The final solution is used in the tests for carbonates.

1 mL of *1 M hydrochloric acid* is equivalent to 37.05 mg of $Ca(OH)_2$.

01/2017:2118

CALCIUM LACTATE

Calcii lactas



$C_6H_{10}CaO_6$ M_r 218.2

DEFINITION

Calcium bis(2-hydroxypropanoate) or mixture of calcium (2*R*)-, (2*S*)- and (2*RS*)-2-hydroxypropanoates.

Content: 98.0 per cent to 102.0 per cent (dried substance).

CHARACTERS

Appearance: white or almost white, crystalline or granular powder.

Solubility: soluble in water, freely soluble in boiling water, very slightly soluble in ethanol (96 per cent).

IDENTIFICATION

A. Loss on drying (see Tests).

B. It gives the reaction of lactates (*2.3.1*).

C. It gives reaction (b) of calcium (*2.3.1*).

TESTS

Solution S. Dissolve 5.0 g with heating in *carbon dioxide-free water R* prepared from *distilled water R*, allow to cool and dilute to 100 mL with the same solvent.

Appearance of solution. Solution S is not more opalescent than reference suspension II (*2.2.1*) and not more intensely coloured than reference solution BY_6 (*2.2.2, Method II*).

Acidity or alkalinity. To 10 mL of solution S add 0.1 mL of *phenolphthalein solution R* and 0.5 mL of *0.01 M hydrochloric acid*. The solution is colourless. Not more than 2.0 mL of *0.01 M sodium hydroxide* is required to change the colour of the indicator to pink.

Chlorides (*2.4.4*): maximum 200 ppm.

Dilute 5 mL of solution S to 15 mL with *water R*.

Sulfates (*2.4.13*): maximum 400 ppm.

Dilute 7.5 mL of solution S to 15 mL with *distilled water R*.

Barium. To 10 mL of solution S add 1 mL of *calcium sulfate solution R*. Allow to stand for 15 min. Any opalescence in the solution is not more intense than that in a mixture of 1 mL of *distilled water R* and 10 mL of solution S.

Iron (*2.4.9*): maximum 50 ppm.

Dilute 4 mL of solution S to 10 mL with *water R*.

Magnesium and alkali salts: maximum 1 per cent.

To 20 mL of solution S add 20 mL of *water R*, 2 g of *ammonium chloride R* and 2 mL of *dilute ammonia R1*. Heat to boiling and rapidly add 40 mL of hot *ammonium oxalate solution R*. Allow to stand for 4 h, dilute to 100.0 mL with *water R* and filter. To 50.0 mL of the filtrate add 0.5 mL of *sulfuric acid R*. Evaporate to dryness and ignite the residue to constant mass at 600 ± 50 °C. The residue weighs a maximum of 5 mg.

Loss on drying (*2.2.32*): maximum 3.0 per cent, determined on 0.500 g by drying in an oven at 125 °C.

ASSAY

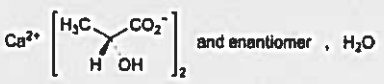
Dissolve 0.200 g in *water R* and dilute to 300 mL with the same solvent. Carry out the complexometric titration of calcium (*2.5.11*).

1 mL of *0.1 M sodium edetate* is equivalent to 21.82 mg of $C_6H_{10}CaO_6$.

01/2017:2117

CALCIUM LACTATE MONOHYDRATE

Calcii lactas monohydricus



$C_6H_{10}CaO_6,H_2O$ M_r 236.0

DEFINITION

Calcium bis(2-hydroxypropanoate) or mixture of calcium (2*R*)-, (2*S*)- and (2*RS*)-2-hydroxypropanoates monohydrates.

Content: 98.0 per cent to 102.0 per cent (dried substance).

CHARACTERS

Appearance: white or almost white, crystalline or granular powder.

Solubility: soluble in water, freely soluble in boiling water, very slightly soluble in ethanol (96 per cent).

IDENTIFICATION

A. Loss on drying (see Tests).

B. It gives the reaction of lactates (*2.3.1*).

C. It gives reaction (b) of calcium (*2.3.1*).

TESTS

Solution S. Dissolve 5.4 g (equivalent to 5.0 g of the dried substance) with heating in *carbon dioxide-free water R* prepared from *distilled water R*, allow to cool and dilute to 100 mL with the same solvent.

Appearance of solution. Solution S is not more opalescent than reference suspension II (*2.2.1*) and not more intensely coloured than reference solution BY_6 (*2.2.2, Method II*).

Acidity or alkalinity. To 10 mL of solution S add 0.1 mL of *phenolphthalein solution R* and 0.5 mL of *0.01 M hydrochloric acid*. The solution is colourless. Not more than 2.0 mL of *0.01 M sodium hydroxide* is required to change the colour of the indicator to pink.

Chlorides (*2.4.4*): maximum 200 ppm.

Dilute 5 mL of solution S to 15 mL with *water R*.

Sulfates (*2.4.13*): maximum 400 ppm.

Dilute 7.5 mL of solution S to 15 mL with *distilled water R*.

Barium. To 10 mL of solution S add 1 mL of *calcium sulfate solution R*. Allow to stand for 15 min. Any opalescence in the solution is not more intense than that in a mixture of 1 mL of *distilled water R* and 10 mL of solution S.

Iron (*2.4.9*): maximum 50 ppm.

Dilute 4 mL of solution S to 10 mL with *water R*.

Magnesium and alkali salts: maximum 1 per cent.

To 20 mL of solution S add 20 mL of *water R*, 2 g of *ammonium chloride R* and 2 mL of *dilute ammonia R1*. Heat to boiling and rapidly add 40 mL of hot *ammonium oxalate solution R*. Allow to stand for 4 h, dilute to 100.0 mL with *water R* and filter. To 50.0 mL of the filtrate add 0.5 mL of *sulfuric acid R*. Evaporate to dryness and ignite the residue to constant mass at 600 ± 50 °C. The residue weighs a maximum of 5 mg.

Loss on drying (*2.2.32*): 5.0 per cent to 8.0 per cent, determined on 0.500 g by drying in an oven at 125 °C.

ASSAY

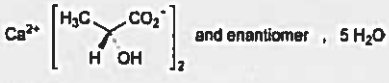
Dissolve a quantity equivalent to 0.200 g of the dried substance in *water R* and dilute to 300 mL with the same solvent. Carry out the complexometric titration of calcium (*2.5.11*).

1 mL of *0.1 M sodium edetate* is equivalent to 21.82 mg of $C_6H_{10}CaO_6$.

01/2017:0468

CALCIUM LACTATE PENTAHYDRATE

Calcii lactas pentahydricus

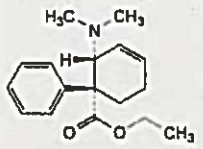


$C_6H_{10}CaO_6,5H_2O$ M_r 308.3

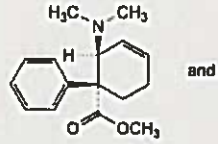
DEFINITION

Calcium bis(2-hydroxypropanoate) or mixture of calcium (2*R*)-, (2*S*)- and (2*RS*)-2-hydroxypropanoates pentahydrates.

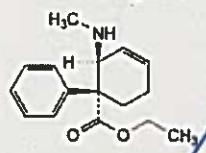
Content: 98.0 per cent to 102.0 per cent (dried substance).



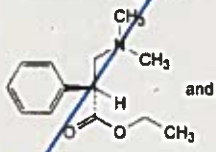
A. ethyl (1*RS*,2*RS*)-2-(dimethylamino)-1-phenylcyclohex-3-enecarboxylate,



B. methyl (1*RS*,2*SR*)-2-(dimethylamino)-1-phenylcyclohex-3-enecarboxylate,



C. ethyl (1*RS*,2*SR*)-2-(methylamino)-1-phenylcyclohex-3-enecarboxylate,

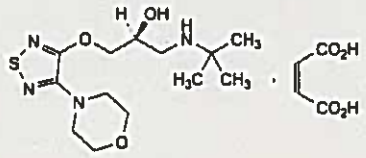


D. ethyl (2*RS*)-3-(dimethylamino)-2-phenylpropanoate.

01/2017:0572

TIMOLOL MALEATE

Timololi maleas



$C_{17}H_{28}N_4O_7S$ M_r 432.5
[26921-17-5]

DEFINITION

(2*S*)-1-[(1,1-Dimethylethyl)amino]-3-[[4-(morpholin-4-yl)-1,2,5-thiadiazol-3-yl]oxy]propan-2-ol (*Z*)-butenedioate.

Content: 98.5 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance: white or almost white, crystalline powder or colourless crystals.

Solubility: soluble in water and in ethanol (96 per cent).

mp: about 199 °C, with decomposition.

IDENTIFICATION

First identification: A, B.

Second identification: A, C, D.

A. Specific optical rotation (2.2.7): − 6.2 to − 5.7.
Dissolve 1.000 g in *1 M hydrochloric acid* and dilute to 10.0 mL with the same acid.

B. Infrared absorption spectrophotometry (2.2.24).
Comparison: *timolol maleate CRS*.

C. Thin-layer chromatography (2.2.27).
Test solution. Dissolve 5 mg of the substance to be examined in *methanol R* and dilute to 5 mL with the same solvent.
Reference solution. Dissolve 5 mg of *timolol maleate CRS* in *methanol R* and dilute to 5 mL with the same solvent.
Plate: *TLC silica gel* GF_{254} *plate R*.
Mobile phase: *concentrated ammonia R, methanol R, methylene chloride R* (1:20:80 *V/V/V*).
Application: 10 µL.
Development: over 2/3 of the plate.
Drying: in air.
Detection: expose to iodine vapour for 2 h.
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. Triturate 0.1 g with a mixture of 1 mL of *dilute sodium hydroxide solution R* and 3 mL of *water R*. Shake with 3 quantities, each of 5 mL, of *ether R*. To 0.1 mL of the aqueous layer add a solution containing 10 mg of *resorcinol R* in 3 mL of *sulfuric acid R*. Heat on a water-bath for 15 min; no violet-red colour develops. Neutralise the remainder of the aqueous layer with *dilute sulfuric acid R* and add 1 mL of *bromine water R*. Heat on a water-bath for 15 min, then heat to boiling and cool. To 0.2 mL of this solution add a solution containing 10 mg of *resorcinol R* in 3 mL of *sulfuric acid R*. Heat on a water-bath for 15 min; a violet-red colour develops. Add 0.2 mL of a 100 g/L solution of *potassium bromide R* and heat for 5 min on a water-bath; the colour becomes violet-blue.

TESTS

Solution S. Dissolve 0.5 g in *carbon dioxide-free water R* and dilute to 25 mL with the same solvent.

Appearance of solution. Solution S is clear (2.2.1) and not more intensely coloured than reference solution B_8 (2.2.2, *Method II*).

pH (2.2.3): 3.8 to 4.3 for solution S.

Enantiomeric purity. Liquid chromatography (2.2.29). *Carry out the test protected from actinic light.*

Solvent mixture: *methylene chloride R, 2-propanol R* (10:30 *V/V*).

Test solution. Dissolve 30.0 mg of the substance to be examined in the solvent mixture and dilute to 10.0 mL with the solvent mixture.

Reference solution (a). Dissolve 30 mg of *timolol maleate CRS* in the solvent mixture and dilute to 10 mL with the solvent mixture.

Reference solution (b). Dissolve 3 mg of *(R)-timolol CRS* (impurity A) in the solvent mixture and dilute to 10.0 mL with the solvent mixture. Dilute 1.0 mL of the solution to 10.0 mL with the solvent mixture.

Reference solution (c). Dilute 1 mL of reference solution (a) to 100 mL with the solvent mixture. Mix 1 mL of this solution with 1 mL of reference solution (b).

Reference solution (d). Dilute 1.0 mL of the test solution to 100.0 mL with the solvent mixture.

Column:
- *size*: *l* = 0.25 m, Ø ≈ 4.6 mm;
- *stationary phase*: *cellulose derivative of silica gel for chiral separation R* (5 µm).

Mobile phase: *diethylamine R, 2-propanol R, hexane R* (2:40:960 *V/V/V*).

Flow rate: 1 mL/min.

Detection: spectrophotometer at 297 nm.

Injection: 5 µL.

Monographs

Elution order: impurity A is eluted first.

System suitability:

- *resolution*: minimum 4.0 between the peaks due to impurity A and the (*S*)-enantiomer in the chromatogram obtained with reference solution (c);
- the retention times of the principal peaks due to the (*S*)-enantiomer in the chromatograms obtained with the test solution and reference solution (a) are identical.

Limit:

- *impurity A*: not more than the area of the principal peak in the chromatogram obtained with reference solution (d) (1.0 per cent).

Related substances. Liquid chromatography (*2.2.29*).

Test solution. Dissolve 0.100 g of the substance to be examined in mobile phase A and dilute to 20 mL with mobile phase A.

Reference solution (a). Dilute 1.0 mL of the test solution to 100.0 mL with mobile phase A. Dilute 1.0 mL of this solution to 10.0 mL with mobile phase A.

Reference solution (b). Dissolve 3 mg of *timolol impurity F CRS* in *methanol R* and dilute to 20.0 mL with the same solvent. Dilute 1.0 mL of the solution to 10.0 mL with mobile phase A (solution A). Dissolve the contents of a vial of *timolol for system suitability CRS* (containing impurities B, C and D) in 1.0 mL of solution A.

Reference solution (c). Dissolve 2 mg of the substance to be examined and 20 mg of *maleic acid R* in 10 mL of *acetonitrile R*. Evaporate 1 mL of the solution to dryness under a stream of *nitrogen R* in an amber glass vial. Heat the open vial at 105 °C for 1 h. Reconstitute the residue with 1.0 mL of mobile phase A (*in situ* preparation of impurity E).

Column:

- *size*: *l* = 0.150 m, Ø = 3.9 mm;
- *stationary phase*: *octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase:

- *mobile phase A*: mixture of equal volumes of *methanol R* and a 4.32 g/L solution of *sodium octanesulfonate R* previously adjusted to pH 3.0 with *glacial acetic acid R*;
- *mobile phase B*: *methanol R*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 10	97.5	2.5
10 - 11	97.5 → 70	2.5 → 30
11 - 20	70	30

Flow rate: 1.2 mL/min.

Detection: spectrophotometer at 295 nm.

Injection: 20 µL.

Identification of impurities: use the chromatogram supplied with *timolol for system suitability CRS* and the chromatogram obtained with reference solution (b) to identify the peaks due to impurities B, C, D and F; use the chromatogram obtained with reference solution (c) to identify the peak due to impurity E.

Relative retention with reference to timolol (retention time = about 7.5 min): maleic acid = about 0.1; impurity D = about 0.3; impurity E = about 0.4; impurity B = about 0.7; impurity F = about 0.8; impurity C = about 2.1.

System suitability: reference solution (b):

- *resolution*: minimum 1.5 between the peaks due to impurities B and F.

Limits:

- *correction factor*: for the calculation of content, multiply the peak area of impurity D by 0.6;
- *impurities B, C, D, E, F*: for each impurity, not more than twice the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 per cent);
- *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.10 per cent);
- *total*: not more than 4 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.4 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); disregard any peak due to maleic acid.

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

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

ASSAY

Dissolve 0.350 g in 60 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 43.25 mg of $C_{17}H_{28}N_4O_7S$.

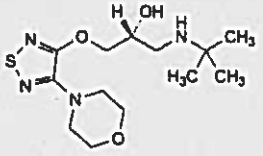
STORAGE

Protected from light.

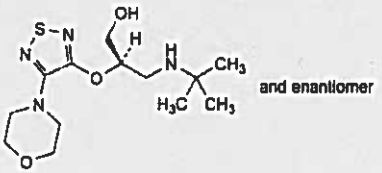
IMPURITIES

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

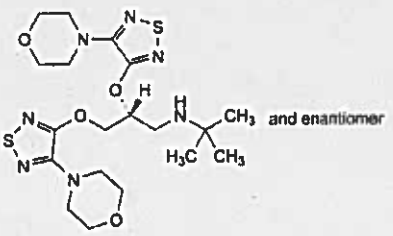
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph *Substances for pharmaceutical 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*): *G, H, I, J.*



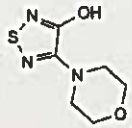
A. (2*R*)-1-[(1,1-dimethylethyl)amino]-3-[[4-(morpholin-4-yl)-1,2,5-thiadiazol-3-yl]oxy]propan-2-ol ((*R*)-timolol),



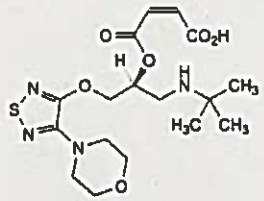
B. (2*RS*)-3-[(1,1-dimethylethyl)amino]-2-[[4-(morpholin-4-yl)-1,2,5-thiadiazol-3-yl]oxy]propan-1-ol,



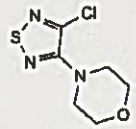
C. (2*RS*)-*N*-(1,1-dimethylethyl)-2,3-bis[[4-(morpholin-4-yl)-1,2,5-thiadiazol-3-yl]oxy]propan-1-amine,



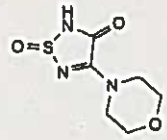
D. 4-(morpholin-4-yl)-1,2,5-thiadiazol-3-ol,



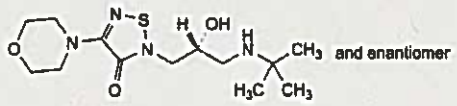
E. (2*Z*)-4-[(1*S*)-1-[[(1,1-dimethylethyl)amino]methyl]-2-[[4-(morpholin-4-yl)-1,2,5-thiadiazol-3-yl]oxy]ethoxy]-4-oxobut-2-enoic acid,



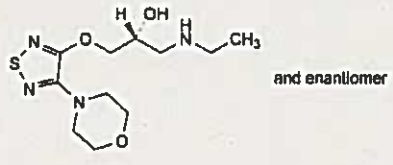
F. 4-(4-chloro-1,2,5-thiadiazol-3-yl)morpholine,



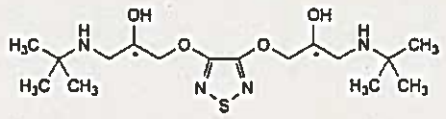
G. 4-(morpholin-4-yl)-1,2,5-thiadiazol-3(2*H*)-one 1-oxide,



H. 2-[(2*RS*)-3-[(1,1-dimethylethyl)amino]-2-hydroxypropyl]-4-(morpholin-4-yl)-1,2,5-thiadiazol-3(2*H*)-one,



I. (2*RS*)-1-(ethylamino)-3-[[4-(morpholin-4-yl)-1,2,5-thiadiazol-3-yl]oxy]propan-2-ol,

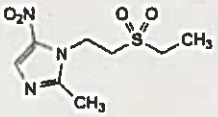


J. 1,1'-[1,2,5-thiadiazol-3,4-diylbis(oxy)]bis[3-[(1,1-dimethylethyl)amino]propan-2-ol].

01/2017:1051

TINIDAZOLE

Tinidazolum



$C_8H_{13}N_3O_4S$ M_r 247.3
[19387-91-8]

DEFINITION

1-[2-(Ethylsulfonyl)ethyl]-2-methyl-5-nitro-1*H*-imidazole.

Content: 98.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance: almost white or pale yellow, crystalline powder.

Solubility: practically insoluble in water, soluble in acetone and in methylene chloride, sparingly soluble in methanol.

IDENTIFICATION

First identification: A, C.

Second identification: A, B, D, E.

A. Melting point (*2.2.14*): 125 °C to 128 °C.

B. Ultraviolet and visible absorption spectrophotometry (*2.2.25*).

Test solution. Dissolve 10.0 mg in *methanol R* and dilute to 100.0 mL with the same solvent. Dilute 1.0 mL of this solution to 10.0 mL with *methanol R*.

Spectral range: 220-350 nm.

Absorption maximum: at 310 nm.

Specific absorbance at the absorption maximum: 340 to 360.

C. Infrared absorption spectrophotometry (*2.2.24*).

Comparison: *tinidazole CRS*.

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

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

Reference solution. Dissolve 20 mg of *tinidazole CRS* in *methanol R* and dilute to 10 mL with the same solvent.

Plate: *TLC silica gel GF_{254} plate R*.

Pretreatment: heat at 110 °C for 1 h and allow to cool.

Mobile phase: *butanol R*, *ethyl acetate R* (25:75 *V/V*).

Application: 10 µL.

Development: over 2/3 of the plate.

Drying: in air.

Detection: examine in ultraviolet light at 254 nm.

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

E. To about 10 mg add about 10 mg of *zinc powder R*, 0.3 mL of *hydrochloric acid R* and 1 mL of *water R*. Heat in a water-bath for 5 min and cool. The solution gives the reaction of primary aromatic amines (*2.3.1*).

Monographs

Related substances. Examine by thin-layer chromatography (*2.2.27*), using *silica gel G R* as the coating substance.

Test solution (a). Dissolve 0.2 g of the substance to be examined in *methanol R* and dilute to 10 mL with the same solvent.

Test solution (b). Dilute 1 mL of test solution (a) to 10 mL with *methanol R*.

Reference solution (a). Dissolve 25 mg of *ephedrine hydrochloride CRS* in *methanol R* and dilute to 10 mL with the same solvent.

Reference solution (b). Dilute 1.0 mL of test solution (a) to 200 mL with *methanol R*.

Apply separately to the plate 10 µL of each solution. Develop over a path of 15 cm using a mixture of 5 volumes of *chloroform R*, 15 volumes of *concentrated ammonia R* and 80 volumes of *2-propanol R*. Allow the plate to dry in air and spray with *ninhydrin solution R*. Heat at 110 °C for 5 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). Disregard any spot of lighter colour than the background.

Chlorides. Dissolve 0.18 g in 10 mL of *water R*. Add 5 mL of *dilute nitric acid R* and 0.5 mL of *silver nitrate solution R1*. Allow to stand for 2 min, protected from bright light. Any opalescence in the solution is not more intense than that in a standard prepared at the same time and in the same manner using 10 mL of *chloride standard solution (5 ppm Cl) R*, 5 mL of *dilute nitric acid R* and 0.5 mL of *silver nitrate solution R1* (280 ppm).

Water (*2.5.12*): 4.5 per cent to 5.5 per cent, determined on 0.300 g by the semi-micro determination of water.

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

ASSAY

Dissolve 0.200 g in 5 mL of *alcohol R* and add 20.0 mL of *0.1 M hydrochloric acid*. Using 0.05 mL of *methyl red solution R* as indicator, titrate with *0.1 M sodium hydroxide* until a yellow colour is obtained.

1 mL of *0.1 M hydrochloric acid* is equivalent to 16.52 mg of $C_{10}H_{15}NO$.

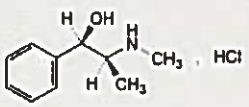
STORAGE

Store protected from light.

01/2008:0487
corrected 6.0

EPHEDRINE HYDROCHLORIDE

Ephedrini hydrochloridum



$C_{10}H_{16}ClNO$ M_r 201.7
[50-98-6]

DEFINITION

(1*R*,2*S*)-2-(Methylamino)-1-phenylpropan-1-ol hydrochloride.

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

CHARACTERS

Appearance: white or almost white, crystalline powder or colourless crystals.

Solubility: freely soluble in water, soluble in ethanol (96 per cent).

mp: about 219 °C.

IDENTIFICATION

First identification: B, E.

Second identification: A, C, D, E.

A. Specific optical rotation (see Tests).

B. Infrared absorption spectrophotometry (*2.2.24*).
Comparison: ephedrine hydrochloride CRS.

C. Thin-layer chromatography (*2.2.27*).
Test solution. Dissolve 20 mg of the substance to be examined in *methanol R* and dilute to 10 mL with the same solvent.
Reference solution. Dissolve 10 mg of *ephedrine hydrochloride CRS* in *methanol R* and dilute to 5 mL with the same solvent.
Plate: TLC silica gel plate R.
Mobile phase: methylene chloride R, concentrated ammonia R, 2-propanol R (5:15:80 *V/V/V*).
Application: 10 µL.
Development: over 2/3 of the plate.
Drying: in air.
Detection: spray with *ninhydrin solution R*; heat at 110 °C for 5 min.
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. To 0.1 mL of solution S (see Tests) add 1 mL of *water R*, 0.2 mL of *copper sulfate solution R* and 1 mL of *strong sodium hydroxide solution R*. A violet colour is produced. Add 2 mL of *methylene chloride R* and shake. The lower (organic) layer is dark grey and the upper (aqueous) layer is blue.

E. To 5 mL of solution S (see Tests) add 5 mL of *water R*. The solution gives reaction (a) of chlorides (*2.3.1*).

TESTS

Solution S. Dissolve 5.00 g in *distilled water R* and dilute to 50.0 mL with the same solvent.

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

Acidity or alkalinity. To 10 mL of solution S add 0.1 mL of *methyl red solution R* and 0.2 mL of *0.01 M sodium hydroxide*. The solution is yellow. Add 0.4 mL of *0.01 M hydrochloric acid*. The solution is red.

Specific optical rotation (*2.2.7*): − 33.5 to − 35.5 (dried substance).

Dilute 12.5 mL of solution S to 25.0 mL with *water R*.

Related substances. Liquid chromatography (*2.2.29*).

Test solution. Dissolve 75 mg of the substance to be examined in the mobile phase and dilute to 10 mL with the mobile phase.

Reference solution (a). Dilute 2.0 mL of the test solution to 100.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 10.0 mL with the mobile phase.

Reference solution (b). Dissolve 5 mg of the substance to be examined and 5 mg of *pseudoephedrine hydrochloride CRS* in the mobile phase and dilute to 50 mL with the mobile phase.

Column:
- *size*: *l* = 0.15 m, Ø = 4.6 mm;
- *stationary phase*: spherical *phenylsilyl silica gel for chromatography R* (3 µm).

Mobile phase: mix 6 volumes of *methanol R* and 94 volumes of a 11.6 g/L solution of *ammonium acetate R* adjusted to pH 4.0 with *glacial acetic acid R*.

Flow rate: 1.0 mL/min.

Detection: spectrophotometer at 257 nm.

Injection: 20 µL.

Run time: 2.5 times the retention time of ephedrine.

Relative retention with reference to ephedrine (retention time = about 8 min): impurity B = about 1.1; impurity A = about 1.4.

System suitability: reference solution (b):

- *resolution*: minimum 2.0 between the peaks due to ephedrine and impurity B.

Limits:

- *correction factor*: for the calculation of content, multiply the peak area of impurity A by 0.4;
- *impurity A*: not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 per cent);
- *unspecified impurities*: for each impurity, not more than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.1 per cent);
- *sum of impurities other than A*: not more than 2.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.5 per cent);
- *disregard limit*: 0.25 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

Sulfates (*2.4.13*): maximum 100 ppm, determined on solution S.

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

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

ASSAY

Dissolve 0.150 g in 50 mL of *ethanol (96 per cent) R* and add 5.0 mL of *0.01 M hydrochloric acid*. Carry out a potentiometric titration (*2.2.20*), using *0.1 M sodium hydroxide*. Read the volume added between the 2 points of inflexion.

1 mL of *0.1 M sodium hydroxide* is equivalent to 20.17 mg of $C_{10}H_{16}ClNO$.

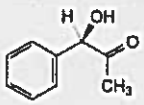
STORAGE

Protected from light.

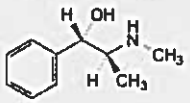
IMPURITIES

Specified impurities: A.

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*): B.



A. (–)-(1*R*)-1-hydroxy-1-phenylpropan-2-one,

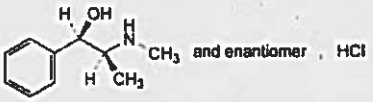


B. (1*S*,2*S*)-2-(methylamino)-1-phenylpropan-1-ol (pseudoephedrine).

01/2008:0715
corrected 6.0

EPHEDRINE HYDROCHLORIDE, RACEMIC

Ephedrini racemici hydrochloridum



$C_{10}H_{16}ClNO$ M_r 201.7
[134-71-4]

DEFINITION

Racemic ephedrine hydrochloride contains not less than 99.0 per cent and not more than the equivalent of 101.0 per cent of (1*RS*,2*SR*)-2-(methylamino)-1-phenylpropan-1-ol hydrochloride, calculated with reference to the dried substance.

CHARACTERS

A white or almost white, crystalline powder or colourless crystals, freely soluble in water, soluble in ethanol (96 per cent).

It melts at about 188 °C.

IDENTIFICATION

First identification: B, E.

Second identification: A, C, D, E.

A. Optical rotation (see Tests).

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

C. Examine the chromatograms obtained in the test for related 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. To 0.1 mL of solution S (see Tests) add 1 mL of *water R*, 0.2 mL of *copper sulfate solution R* and 1 mL of *strong sodium hydroxide solution R*. A violet colour is produced. Add 2 mL of *ether R* and shake. The ether layer is purple and the aqueous layer is blue.

E. To 5 mL of solution S add 5 mL of *water R*. The solution gives reaction (a) of chlorides (*2.3.1*).

TESTS

Solution S. Dissolve 5.00 g in *distilled water R* and dilute to 50.0 mL with the same solvent.

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

Acidity or alkalinity. To 10 mL of solution S add 0.1 mL of *methyl red solution R* and 0.1 mL of *0.01 M sodium hydroxide*; the solution is yellow. Add 0.2 mL of *0.01 M hydrochloric acid*; the solution is red.

Optical rotation (*2.2.7*): + 0.2° to – 0.2°, determined on solution S.

Related substances. Examine by thin-layer chromatography (*2.2.27*), using *silica gel G R* as the coating substance.

Test solution (a). Dissolve 0.20 g of the substance to be examined in *methanol R* and dilute to 10 mL with the same solvent.

Monographs E

2.3. IDENTIFICATION

01/2008:20301

2.3.1. IDENTIFICATION REACTIONS OF IONS AND FUNCTIONAL GROUPS

ACETATES

a) Heat the substance to be examined with an equal quantity of *oxalic acid R*. Acid vapours with the characteristic odour of acetic acid are liberated, showing an acid reaction (*2.2.4*).

b) Dissolve about 30 mg of the substance to be examined in 3 mL of *water R* or use 3 mL of the prescribed solution. Add successively 0.25 mL of *lanthanum nitrate solution R*, 0.1 mL of *0.05 M iodine* and 0.05 mL of *dilute ammonia R2*. Heat carefully to boiling. Within a few minutes a blue precipitate is formed or a dark blue colour develops.

ACETYL

In a test-tube about 180 mm long and 18 mm in external diameter, place about 15 mg of the substance to be examined, or the prescribed quantity, and 0.15 mL of *phosphoric acid R*. Close the tube with a stopper through which passes a small test-tube about 100 mm long and 10 mm in external diameter containing *water R* to act as a condenser. On the outside of the smaller tube, hang a drop of *lanthanum nitrate solution R*. Except for substances hydrolysable only with difficulty, place the apparatus in a water-bath for 5 min, then take out the smaller tube. Remove the drop and mix it with 0.05 mL of *0.01 M iodine* on a tile. Add at the edge 0.05 mL of *dilute ammonia R2*. After 1 min to 2 min, a blue colour develops at the junction of the two drops; the colour intensifies and persists for a short time.

For *substances hydrolysable only with difficulty* heat the mixture slowly to boiling over an open flame and then proceed as prescribed above.

ALKALOIDS

Dissolve a few milligrams of the substance to be examined, or the prescribed quantity, in 5 mL of *water R*, add *dilute hydrochloric acid R* until an acid reaction occurs (*2.2.4*), then 1 mL of *potassium iodobismuthate solution R*. An orange or orange-red precipitate is formed immediately.

ALUMINIUM

Dissolve about 15 mg of the substance to be examined in 2 mL of *water R* or use 2 mL of the prescribed solution. Add about 0.5 mL of *dilute hydrochloric acid R* and about 0.5 mL of *thioacetamide reagent R*. No precipitate is formed. Add dropwise *dilute sodium hydroxide solution R*. A gelatinous white precipitate is formed which dissolves on further addition of *dilute sodium hydroxide solution R*. Gradually add *ammonium chloride solution R*. The gelatinous white precipitate is re-formed.

AMINES, PRIMARY AROMATIC

Acidify the prescribed solution with *dilute hydrochloric acid R* and add 0.2 mL of *sodium nitrite solution R*. After 1 min to 2 min, add 1 mL of *β-naphthol solution R*. An intense orange or red colour and usually a precipitate of the same colour are produced.

AMMONIUM SALTS

To the prescribed solution add 0.2 g of *magnesium oxide R*. Pass a current of air through the mixture and direct the gas that escapes just beneath the surface of a mixture of 1 mL of *0.1 M hydrochloric acid* and 0.05 mL of *methyl red solution R*. The colour of the indicator changes to yellow. On addition of 1 mL of a freshly prepared 100 g/L solution of *sodium cobaltinitrite R* a yellow precipitate is formed.

AMMONIUM SALTS AND SALTS OF VOLATILE BASES

Dissolve about 20 mg of the substance to be examined in 2 mL of *water R* or use 2 mL of the prescribed solution. Add 2 mL of *dilute sodium hydroxide solution R*. On heating, the solution gives off vapour that can be identified by its odour and by its alkaline reaction (*2.2.4*).

ANTIMONY

Dissolve with gentle heating about 10 mg of the substance to be examined in a solution of 0.5 g of *sodium potassium tartrate R* in 10 mL of *water R* and allow to cool: to 2 mL of this solution, or to 2 mL of the prescribed solution, add *sodium sulfide solution R* dropwise; an orange-red precipitate is formed which dissolves on addition of *dilute sodium hydroxide solution R*.

ARSENIC

Heat 5 mL of the prescribed solution on a water-bath with an equal volume of *hypophosphorous reagent R*. A brown precipitate is formed.

BARBITURATES, NON-NITROGEN SUBSTITUTED

Dissolve about 5 mg of the substance to be examined in 3 mL of *methanol R*, add 0.1 mL of a solution containing 100 g/L of *cobalt nitrate R* and 100 g/L of *calcium chloride R*. Mix and add, with shaking, 0.1 mL of *dilute sodium hydroxide solution R*. A violet-blue colour and precipitate are formed.

BENZOATES

a) To 1 mL of the prescribed solution add 0.5 mL of *ferric chloride solution R1*. A dull-yellow precipitate, soluble in *ether R*, is formed.

b) Place 0.2 g of the substance to be examined, treated if necessary as prescribed, in a test-tube. Moisten with 0.2 mL to 0.3 mL of *sulfuric acid R*. Gently warm the bottom of the tube. A white sublimate is deposited on the inner wall of the tube.

c) Dissolve 0.5 g of the substance to be examined in 10 mL of *water R* or use 10 mL of the prescribed solution. Add 0.5 mL of *hydrochloric acid R*. The precipitate obtained, after crystallisation from warm *water R* and drying *in vacuo*, has a melting point (*2.2.14*) of 120 °C to 124 °C.

BISMUTH

a) To 0.5 g of the substance to be examined add 10 mL of *dilute hydrochloric acid R* or use 10 mL of the prescribed solution. Heat to boiling for 1 min. Cool and filter if necessary. To 1 mL of the solution obtained add 20 mL of *water R*. A white or slightly yellow precipitate is formed which on addition of 0.05 mL to 0.1 mL of *sodium sulfide solution R* turns brown.

b) To about 45 mg of the substance to be examined add 10 mL of *dilute nitric acid R* or use 10 mL of the prescribed solution. Boil for 1 min. Allow to cool and filter if necessary. To 5 mL of the solution obtained add 2 mL of a 100 g/L solution of *thiourea R*. A yellowish-orange colour or an orange precipitate is formed. Add 4 mL of a 25 g/L solution of *sodium fluoride R*. The solution is not decolorised within 30 min.

BROMIDES

a) Dissolve in 2 mL of *water R* a quantity of the substance to be examined equivalent to about 3 mg of bromide (Br^-) or use 2 mL of the prescribed solution. Acidify with *dilute nitric acid R* and add 0.4 mL of *silver nitrate solution R1*. Shake and allow to stand. A curdled, pale yellow precipitate is formed. Centrifuge and wash the precipitate with three quantities, each of 1 mL, of *water R*. Carry out this operation rapidly in subdued light disregarding the fact that the supernatant solution may not become perfectly clear. Suspend the precipitate obtained in 2 mL of *water R* and add 1.5 mL of *ammonia R*. The precipitate dissolves with difficulty.

b) Introduce into a small test-tube a quantity of the substance to be examined equivalent to about 5 mg of bromide (Br^-) or the prescribed quantity. Add 0.25 mL of *water R*, about 75 mg of *lead dioxide R*, 0.25 mL of *acetic acid R* and shake gently. Dry the inside of the upper part of the test-tube with a piece of filter paper and allow to stand for 5 min. Prepare a strip of suitable filter paper of appropriate size. Impregnate it by capillarity, by dipping the tip in a drop of *decolorised fuchsin solution R* and introduce the impregnated part immediately into the tube. Starting from the tip, a violet colour appears within 10 s that is clearly distinguishable from the red colour of fuchsin, which may be visible on a small area at the top of the impregnated part of the paper strip.

CALCIUM

a) To 0.2 mL of a neutral solution containing a quantity of the substance to be examined equivalent to about 0.2 mg of calcium (Ca^{2+}) per millilitre or to 0.2 mL of the prescribed solution add 0.5 mL of a 2 g/L solution of *glyoxalhydroxyanil R* in *ethanol (96 per cent) R*, 0.2 mL of *dilute sodium hydroxide solution R* and 0.2 mL of *sodium carbonate solution R*. Shake with 1 mL to 2 mL of *chloroform R* and add 1 mL to 2 mL of *water R*. The chloroform layer is coloured red.

b) Dissolve about 20 mg of the substance to be examined or the prescribed quantity in 5 mL of *acetic acid R*. Add 0.5 mL of *potassium ferrocyanide solution R*. The solution remains clear. Add about 50 mg of *ammonium chloride R*. A white, crystalline precipitate is formed.

CARBONATES AND BICARBONATES

Introduce into a test-tube 0.1 g of the substance to be examined and suspend in 2 mL of *water R* or use 2 mL of the prescribed solution. Add 3 mL of *dilute acetic acid R*. Close the tube immediately using a stopper fitted with a glass tube bent twice at right angles. The solution or the suspension becomes effervescent and gives off a colourless and odourless gas. Heat gently and collect the gas in 5 mL of *barium hydroxide solution R*. A white precipitate is formed that dissolves on addition of an excess of *hydrochloric acid R1*.

CHLORIDES

a) Dissolve in 2 mL of *water R* a quantity of the substance to be examined equivalent to about 2 mg of chloride (Cl^-) or use 2 mL of the prescribed solution. Acidify with *dilute nitric acid R* and add 0.4 mL of *silver nitrate solution R1*. Shake and allow to stand. A curdled, white precipitate is formed. Centrifuge and wash the precipitate with three quantities, each of 1 mL, of *water R*. Carry out this operation rapidly in subdued light, disregarding the fact that the supernatant solution may not become perfectly clear. Suspend the precipitate in 2 mL of *water R* and add 1.5 mL of *ammonia R*. The precipitate dissolves easily with the possible exception of a few large particles which dissolve slowly.

b) Introduce into a test-tube a quantity of the substance to be examined equivalent to about 15 mg of chloride (Cl^-) or the prescribed quantity. Add 0.2 g of *potassium dichromate R* and 1 mL of *sulfuric acid R*. Place a filter-paper strip impregnated with 0.1 mL of *diphenylcarbazide solution R* over the opening of the test-tube. The paper turns violet-red. The impregnated paper must not come into contact with the potassium dichromate.

CITRATES

Dissolve in 5 mL of *water R* a quantity of the substance to be examined equivalent to about 50 mg of citric acid or use 5 mL of the prescribed solution. Add 0.5 mL of *sulfuric acid R* and 1 mL of *potassium permanganate solution R*. Warm until the colour of the permanganate is discharged. Add 0.5 mL of a 100 g/L solution of *sodium nitroprusside R* in *dilute sulfuric acid R* and 4 g of *sulfamic acid R*. Make alkaline with *concentrated ammonia R*, added dropwise until all the sulfamic acid has dissolved. Addition of an excess of *concentrated ammonia R* produces a violet colour, turning to violet-blue.

ESTERS

To about 30 mg of the substance to be examined or the prescribed quantity add 0.5 mL of a 70 g/L solution of *hydroxylamine hydrochloride R* in *methanol R* and 0.5 mL of a 100 g/L solution of *potassium hydroxide R* in *ethanol (96 per cent) R*. Heat to boiling, cool, acidify with *dilute hydrochloric acid R* and add 0.2 mL of *ferric chloride solution R1* diluted ten times. A bluish-red or red colour is produced.

IODIDES

a) Dissolve a quantity of the substance to be examined equivalent to about 4 mg of iodide (I^-) in 2 mL of *water R* or use 2 mL of the prescribed solution. Acidify with *dilute nitric acid R* and add 0.4 mL of *silver nitrate solution R1*. Shake and allow to stand. A curdled, pale-yellow precipitate is formed. Centrifuge and wash with three quantities, each of 1 mL, of *water R*. Carry out this operation rapidly in subdued light disregarding the fact that the supernatant solution may not become perfectly clear. Suspend the precipitate in 2 mL of *water R* and add 1.5 mL of *ammonia R*. The precipitate does not dissolve.

b) To 0.2 mL of a solution of the substance to be examined containing about 5 mg of iodide (I^-) per millilitre, or to 0.2 mL of the prescribed solution, add 0.5 mL of *dilute sulfuric acid R*, 0.1 mL of *potassium dichromate solution R*, 2 mL of *water R* and 2 mL of *chloroform R*. Shake for a few seconds and allow to stand. The chloroform layer is coloured violet or violet-red.

IRON

a) Dissolve a quantity of the substance to be examined equivalent to about 10 mg of iron (Fe^{2+}) in 1 mL of *water R* or use 1 mL of the prescribed solution. Add 1 mL of *potassium ferricyanide solution R*. A blue precipitate is formed that does not dissolve on addition of 5 mL of *dilute hydrochloric acid R*.

b) Dissolve a quantity of the substance to be examined equivalent to about 1 mg of iron (Fe^{3+}) in 30 mL of *water R*. To 3 mL of this solution or to 3 mL of the prescribed solution, add 1 mL of *dilute hydrochloric acid R* and 1 mL of *potassium thiocyanate solution R*. The solution is coloured red. Take two portions, each of 1 mL, of the mixture. To one portion add 5 mL of *isoamyl alcohol R* or 5 mL of *ether R*. Shake and allow to stand. The organic layer is coloured pink. To the other portion add 2 mL of *mercuric chloride solution R*. The red colour disappears.

c) Dissolve a quantity of the substance to be examined equivalent to not less than 1 mg of iron (Fe^{3+}) in 1 mL of *water R* or use 1 mL of the prescribed solution. Add 1 mL of *potassium ferrocyanide solution R*. A blue precipitate is formed that does not dissolve on addition of 5 mL of *dilute hydrochloric acid R*.

LACTATES

Dissolve a quantity of the substance to be examined equivalent to about 5 mg of lactic acid in 5 mL of *water R* or use 5 mL of the prescribed solution. Add 1 mL of *bromine water R* and 0.5 mL of *dilute sulfuric acid R*. Heat on a water-bath until the colour is discharged, stirring occasionally with a glass rod. Add 4 g of *ammonium sulfate R* and mix. Add dropwise and without mixing 0.2 mL of a 100 g/L solution of *sodium nitroprusside R* in *dilute sulfuric acid R*. Still without mixing add 1 mL of *concentrated ammonia R*. Allow to stand for 30 min. A dark green ring appears at the junction of the two liquids.

LEAD

a) Dissolve 0.1 g of the substance to be examined in 1 mL of *acetic acid R* or use 1 mL of the prescribed solution. Add 2 mL of *potassium chromate solution R*. A yellow precipitate is formed that dissolves on addition of 2 mL of *strong sodium hydroxide solution R*.

b) Dissolve 50 mg of the substance to be examined in 1 mL of *acetic acid R* or use 1 mL of the prescribed solution. Add 10 mL of *water R* and 0.2 mL of *potassium iodide solution R*. A yellow precipitate is formed. Heat to boiling for 1 min to 2 min. The precipitate dissolves. Allow to cool. The precipitate is re-formed as glistening, yellow plates.

MAGNESIUM

Dissolve about 15 mg of the substance to be examined in 2 mL of *water R* or use 2 mL of the prescribed solution. Add 1 mL of *dilute ammonia R1*. A white precipitate is formed that dissolves on addition of 1 mL of *ammonium chloride solution R*. Add 1 mL of *disodium hydrogen phosphate solution R*. A white crystalline precipitate is formed.

MERCURY

a) Place about 0.1 mL of a solution of the substance to be examined on well-scraped copper foil. A dark-grey stain that becomes shiny on rubbing is formed. Dry the foil and heat in a test-tube. The spot disappears.

b) To the prescribed solution add *dilute sodium hydroxide solution R* until strongly alkaline (*2.2.4*). A dense yellow precipitate is formed (mercuric salts).

NITRATES

To a mixture of 0.1 mL of *nitrobenzene R* and 0.2 mL of *sulfuric acid R*, add a quantity of the powdered substance equivalent to about 1 mg of nitrate (NO_3^-) or the prescribed quantity. Allow to stand for 5 min. Cool in iced water and add slowly and with mixing 5 mL of *water R*, then 5 mL of *strong sodium hydroxide solution R*. Add 5 mL of *acetone R*. Shake and allow to stand. The upper layer is coloured deep violet.

PHOSPHATES (ORTHOPHOSPHATES)

a) To 5 mL of the prescribed solution, neutralised if necessary, add 5 mL of *silver nitrate solution R1*. A yellow precipitate is formed whose colour is not changed by boiling and which dissolves on addition of *ammonia R*.

b) Mix 1 mL of the prescribed solution with 2 mL of *molybdovanadic reagent R*. A yellow colour develops.

POTASSIUM

a) Dissolve 0.1 g of the substance to be examined in 2 mL of *water R* or use 2 mL of the prescribed solution. Add 1 mL of *sodium carbonate solution R* and heat. No precipitate is formed. Add to the hot solution 0.05 mL of *sodium sulfide solution R*. No precipitate is formed. Cool in iced water and add 2 mL of a 150 g/L solution of *tartaric acid R*. Allow to stand. A white crystalline precipitate is formed.

b) Dissolve about 40 mg of the substance to be examined in 1 mL of *water R* or use 1 mL of the prescribed solution. Add 1 mL of *dilute acetic acid R* and 1 mL of a freshly prepared 100 g/L solution of *sodium cobaltinitrite R*. A yellow or orange-yellow precipitate is formed immediately.

SALICYLATES

a) To 1 mL of the prescribed solution add 0.5 mL of *ferric chloride solution R1*. A violet colour is produced that persists after the addition of 0.1 mL of *acetic acid R*.

b) Dissolve 0.5 g of the substance to be examined in 10 mL of *water R* or use 10 mL of the prescribed solution. Add 0.5 mL of *hydrochloric acid R*. The precipitate obtained, after recrystallisation from hot *water R* and drying *in vacuo*, has a melting point (*2.2.14*) of 156 °C to 161 °C.

SILICATES

Mix the prescribed quantity of the substance to be examined in a lead or platinum crucible by means of a copper wire with about 10 mg of *sodium fluoride R* and a few drops of *sulfuric acid R* to give a thin slurry. Cover the crucible with a thin, transparent plate of plastic under which a drop of *water R* is suspended and warm gently. Within a short time a white ring is rapidly formed around the drop of water.

SILVER

Dissolve about 10 mg of the substance to be examined in 10 mL of *water R* or use 10 mL of the prescribed solution. Add 0.3 mL of *hydrochloric acid R1*. A curdled, white precipitate is formed that dissolves on addition of 3 mL of *dilute ammonia R1*.

SODIUM

a) Dissolve 0.1 g of the substance to be examined in 2 mL of *water R* or use 2 mL of the prescribed solution. Add 2 mL of a 150 g/L solution of *potassium carbonate R* and heat to boiling. No precipitate is formed. Add 4 mL of *potassium pyroantimonate solution R* and heat to boiling. Allow to cool in iced water and if necessary rub the inside of the test-tube with a glass rod. A dense white precipitate is formed.

b) Dissolve a quantity of the substance to be examined equivalent to about 2 mg of sodium (Na^+) in 0.5 mL of *water R* or use 0.5 mL of the prescribed solution. Add 1.5 mL of *methoxyphenylacetic reagent R* and cool in ice-water for 30 min. A voluminous, white, crystalline precipitate is formed. Place in water at 20 °C and stir for 5 min. The precipitate does not disappear. Add 1 mL of *dilute ammonia R1*. The precipitate dissolves completely. Add 1 mL of *ammonium carbonate solution R*. No precipitate is formed.

SULFATES

a) Dissolve about 45 mg of the substance to be examined in 5 mL of *water R* or use 5 mL of the prescribed solution. Add 1 mL of *dilute hydrochloric acid R* and 1 mL of *barium chloride solution R1*. A white precipitate is formed.

b) To the suspension obtained during reaction (a), add 0.1 mL of *0.05 M iodine*. The suspension remains yellow (distinction from sulfites and dithionites), but is decolorised by adding dropwise *stannous chloride solution R* (distinction from iodates). Boil the mixture. No coloured precipitate is formed (distinction from selenates and tungstates).

TARTRATES

a) Dissolve about 15 mg of the substance to be examined in 5 mL of *water R* or use 5 mL of the prescribed solution. Add 0.05 mL of a 10 g/L solution of *ferrous sulfate R* and 0.05 mL of *dilute hydrogen peroxide solution R*. A transient yellow colour is produced. After the colour has disappeared add *dilute sodium hydroxide solution R* dropwise. A violet or purple colour is produced.

b) To 0.1 mL of a solution of the substance to be examined containing the equivalent of about 15 mg of tartaric acid per millilitre or to 0.1 mL of the prescribed solution add 0.1 mL of a 100 g/L solution of *potassium bromide R*, 0.1 mL of a 20 g/L solution of *resorcinol R* and 3 mL of *sulfuric acid R*. Heat on a water-bath for 5 min to 10 min. A dark-blue colour develops. Allow to cool and pour the solution into *water R*. The colour changes to red.

XANTHINES

To a few milligrams of the substance to be examined or the prescribed quantity add 0.1 mL of *strong hydrogen peroxide solution R* and 0.3 mL of *dilute hydrochloric acid R*. Heat to dryness on a water-bath until a yellowish-red residue is obtained. Add 0.1 mL of *dilute ammonia R2*. The colour of the residue changes to violet-red.

ZINC

Dissolve 0.1 g of the substance to be examined in 5 mL of *water R* or use 5 mL of the prescribed solution. Add 0.2 mL of *strong sodium hydroxide solution R*. A white precipitate is formed. Add a further 2 mL of *strong sodium hydroxide solution R*. The precipitate dissolves. Add 10 mL of *ammonium chloride solution R*. The solution remains clear. Add 0.1 mL of *sodium sulfide solution R*. A flocculent white precipitate is formed.

UNIVERSITÀ DEGLI STUDI DI TORINO

ESAME DI STATO PER L'ABILITAZIONE ALL'ESERCIZIO DELLA PROFESSIONE DI FARMACISTA

SECONDA SESSIONE 2018

PROVA PRATICA: Dosamento del Farmaco

Cognome e nome.....

20 compresse contenenti aceclofenac (PM: 354,20) ed eccipienti inerti sono state pestate in mortaio, trasferite e sciolte in un matraccio da 250,00 mL; dopo aver portato a volume si è ottenuta la soluzione A.

50,00 mL della soluzione A sono stati prelevati e titolati secondo Eur. Ph. 9. La titolazione ha richiesto 11,143 mL di sodio idrossido 0,1000 M.

75,00 mL di soluzione A sono stati prelevati e trasportati in un matraccio da 200,00 mL. Dopo aver portato a volume si è ottenuta la soluzione B.

Si calcolino:

a) I grammi di aceclofenac contenuti in una compressa.

b) Il % p/v della soluzione B.

c) Ogni compressa dovrebbe contenere 100,00 mg di principio attivo con una variabilità nel titolo di principio attivo del 5,00 %. Si valuti se le compresse analizzate risultano conformi alle specifiche, indicando l'intervallo di peso del principio attivo (espresso in mg) che può essere contenuto in ogni compressa.

Risposte ai quesiti:

a) _____

b) _____

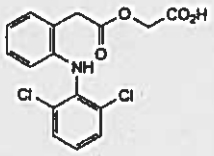
c) _____

N.B. Insieme alla prova al candidato viene fornita copia della monografia ufficiale di Eur. Ph. 9 dell'aceclofenac.

01/2018:1281

ACECLOFENAC

Aceclofenacum



$C_{16}H_{13}Cl_2NO_4$ M_r 354.2
[89796-99-6]

DEFINITION

[[[2-[(2,6-Dichlorophenyl)amino]phenyl]acetyl]oxy]acetic acid.

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

CHARACTERS

Appearance: white or almost white, crystalline powder.

Solubility: practically insoluble in water, freely soluble in acetone, soluble in ethanol (96 per cent).

IDENTIFICATION

First identification: B.

Second identification: A, C.

A. Ultraviolet and visible absorption spectrophotometry (2.2.25).

Test solution. Dissolve 50.0 mg in *methanol R* and dilute to 100.0 mL with the same solvent. Dilute 2.0 mL of the solution to 50.0 mL with *methanol R*.

Spectral range: 220-370 nm.

Absorption maximum: 275 nm.

Specific absorbance at the absorption maximum: 320 to 350.

B. Infrared absorption spectrophotometry (2.2.24).

Comparison: *Ph. Eur. reference spectrum of aceclofenac.*

C. Dissolve about 10 mg in 10 mL of *ethanol (96 per cent) R*. To 1 mL of the solution, add 0.2 mL of a mixture, prepared immediately before use, of equal volumes of a 6 g/L solution of *potassium ferricyanide R* and a 9 g/L solution of *ferric chloride R*. Allow to stand protected from light for 5 min. Add 3 mL of a 10.0 g/L solution of *hydrochloric acid R*. Allow to stand protected from light for 15 min. A blue colour develops and a precipitate is formed.

TESTS

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

Solvent mixture: mobile phase A, mobile phase B (30:70 *V/V*).

Test solution. Dissolve 50.0 mg of the substance to be examined in the solvent mixture and dilute to 25.0 mL with the solvent mixture.

Reference solution (a). Dissolve 21.6 mg of *diclofenac sodium CRS* (impurity A) in the solvent mixture and dilute to 50.0 mL with the solvent mixture.

Reference solution (b). Dilute 2.0 mL of the test solution to 10.0 mL with the solvent mixture.

Reference solution (c). Mix 1.0 mL of reference solution (a) and 1.0 mL of reference solution (b) and dilute to 100.0 mL with the solvent mixture.

Reference solution (d). Dissolve 4.0 mg of *aceclofenac impurity F CRS* in the solvent mixture and dilute to 10.0 mL with the solvent mixture.

Reference solution (e). Dissolve 2.0 mg of *aceclofenac impurity H CRS* in the solvent mixture and dilute to 10.0 mL with the solvent mixture.

Reference solution (f). Mix 1.0 mL of reference solution (b), 1.0 mL of reference solution (d) and 1.0 mL of reference solution (e) and dilute to 100.0 mL with the solvent mixture.

Reference solution (g). Dissolve 5.0 mg of *aceclofenac impurity I CRS* in the solvent mixture and dilute to 50.0 mL with solvent mixture. Dilute 1.0 mL of the solution to 50.0 mL with the solvent mixture.

Reference solution (h). Dissolve 4 mg of *aceclofenac for peak identification CRS* (containing impurities B, C, D, E and G) in 2 mL of the solvent mixture.

Column:

- *size*: *l* = 0.25 m, Ø = 4.6 mm;
- *stationary phase*: spherical *end-capped octadecylsilyl silica gel for chromatography R* (5 µm) with a pore size of 10 nm and a carbon loading of 19 per cent;
- *temperature*: 40 °C.

Mobile phase:

- *mobile phase A*: 1.12 g/L solution of *phosphoric acid R* adjusted to pH 7.0 with a 42 g/L solution of *sodium hydroxide R*;
- *mobile phase B*: *water R, acetonitrile R* (10:90 *V/V*);

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 25	70 → 50	30 → 50
25 - 30	50 → 20	50 → 80
30 - 50	20	80

Flow rate: 1.0 mL/min.

Detection: spectrophotometer at 275 nm.

Injection: 10 µL of the test solution and reference solutions (c), (d), (e), (f), (g) and (h).

Identification of impurities: use the chromatogram obtained with reference solution (c) to identify the peak due to impurity A; use the chromatogram supplied with *aceclofenac for peak identification CRS* and the chromatogram obtained with reference solution (h) to identify the peaks due to impurities B, C, D, E and G; use the chromatogram obtained with reference solution (d) to identify the peak due to impurity F; use the chromatogram obtained with reference solution (e) to identify the peak due to impurity H; use the chromatogram obtained with reference solution (g) to identify the peak due to impurity I.

Relative retention with reference to aceclofenac (retention time = about 11 min): impurity A = about 0.8; impurity G = about 1.3; impurity H = about 1.5; impurity I = about 2.3; impurity D = about 3.1; impurity B = about 3.2; impurity E = about 3.3; impurity C = about 3.5; impurity F = about 3.7.

System suitability: reference solution (c):

- *resolution*: minimum 5.0 between the peaks due to impurity A and aceclofenac.

Limits:

- *impurity A*: not more than the area of the corresponding peak in the chromatogram obtained with reference solution (c) (0.2 per cent);
- *impurities B, C, D, E, G*: for each impurity, not more than the area of the peak due to aceclofenac in the chromatogram obtained with reference solution (f) (0.2 per cent);
- *impurity F*: not more than the area of the corresponding peak in the chromatogram obtained with reference solution (f) (0.2 per cent);
- *impurity H*: not more than 1.5 times the area of the corresponding peak in the chromatogram obtained with reference solution (f) (0.15 per cent);

- *impurity I*: not more than 1.5 times the area of the corresponding peak in the chromatogram obtained with reference solution (g) (0.15 per cent);
- *unspecified impurities*: for each impurity, not more than 0.5 times the area of the peak due to aceclofenac in the chromatogram obtained with reference solution (f) (0.10 per cent);
- *total*: maximum 0.7 per cent;
- *disregard limit*: 0.25 times the area of the peak due to aceclofenac in the chromatogram obtained with reference solution (f) (0.05 per cent).

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

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

ASSAY

Dissolve 0.300 g in 40 mL of *methanol R*. Titrate with *0.1 M sodium hydroxide*, determining the end-point potentiometrically (*2.2.20*).

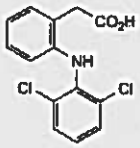
1 mL of *0.1 M sodium hydroxide* is equivalent to 35.42 mg of $C_{16}H_{13}Cl_2NO_4$.

STORAGE

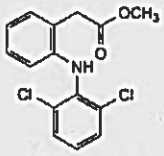
Protected from light.

IMPURITIES

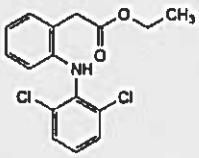
Specified impurities: A, B, C, D, E, F, G, H, I.



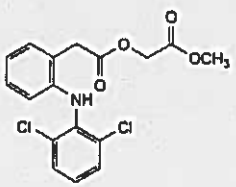
A. [2-[(2,6-dichlorophenyl)amino]phenyl]acetic acid (diclofenac),



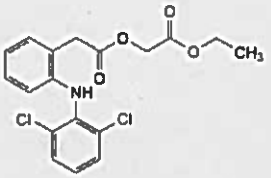
B. methyl [2-[(2,6-dichlorophenyl)amino]phenyl]acetate (methyl ester of diclofenac),



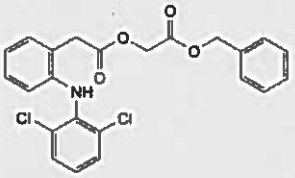
C. ethyl [2-[(2,6-dichlorophenyl)amino]phenyl]acetate (ethyl ester of diclofenac),



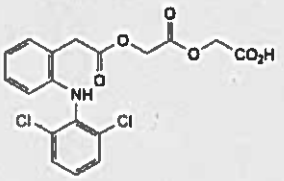
D. methyl [[[2-[(2,6-dichlorophenyl)amino]phenyl]-acetyl]oxy]acetate (methyl ester of aceclofenac),



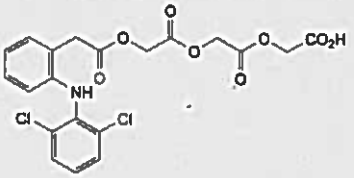
E. ethyl [[[2-[(2,6-dichlorophenyl)amino]phenyl]-acetyl]oxy]acetate (ethyl ester of aceclofenac),



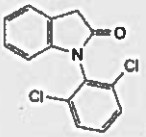
F. benzyl [[[2-[(2,6-dichlorophenyl)amino]phenyl]-acetyl]oxy]acetate (benzyl ester of aceclofenac),



G. [[[[2-[(2,6-dichlorophenyl)amino]phenyl]-acetyl]oxy]acetyl]oxy]acetic acid (acetic aceclofenac),



H. [[[[[[2-[(2,6-dichlorophenyl)amino]phenyl]-acetyl]oxy]acetyl]oxy]acetyl]oxy]acetic acid (diacetic aceclofenac),



I. 1-(2,6-dichlorophenyl)-1,3-dihydro-2*H*-indol-2-one.

01/2018:2903

ACETYLENE INTERMIX (1 PER CENT) IN NITROGEN

Acetylenum (1 per centum) in nitrogenio intermixtum

DEFINITION

A mixture containing 1 per cent *V/V* of acetylene in *Low-oxygen nitrogen (1685)*.

Content: 0.95 per cent *V/V* to 1.05 per cent *V/V* of acetylene (C_2H_2) in nitrogen (N_2).

This monograph applies to acetylene intermix (1 per cent) in nitrogen used in the preparation of lung function test gas mixtures for medicinal use.

Dott. XXXX YYYYYY
Via XXXXXXXX, X
Torino
Tel. XXX/XXXXXXX

Sig./Sig.ra XXXXXX XXXXXXX

Zinco ossido
Talco
Glicerina
Acqua depurata ana 50 g

Preparare 25 g .

Cognome e Nome _____ **Prova n°**_____

SCHEDA DI PREPARAZIONE

Fonte di legittimazione: O Farmacopea_____

M Prescrizione medica del _____N°_____

Forma farmaceutica:_____

Riferimento alla procedura tecnologica_____

Avvertenze e precauzioni:_____

Componenti	*Cod.Interno*	*Lotto**	*Quantità unitarie*	**

** Compilare se preparazione allestita un'unica volta e che dunque non richiede foglio di allestimento.*
*** Barrare se impiegato per motivi tecnici*

Controlli previsti _____

Contenitore _____

Periodo di validità _____

Disciplina di vendita (senza ricetta, RR, RNR, RRM) _____

Metodo di preparazione

_____
_____
_____
_____
_____
_____
_____
_____

OBBLIGO DI REGISTRAZIONE IN USCITA **SÌ** **NO**

Cognome e Nome _____ **Prova n°**_____

SCHEDA RICETTA

Tipologia

□ RR □ RNR □ RRM □ SSN

La ricetta risulta spedibile?
□ sì
□ no perché?

Validità temporale ed eventuale ripetibilità della ricetta in oggetto:

Formalismi obbligatori per il **medico** per la ricetta in oggetto:

Formalismi obbligatori per il **farmacista** per la ricetta in oggetto:

Presenza di:
□ sostanze pericolose per la salute umana
□ sost. stupefacenti e psicotrope □ registrazione registro EU
□ sostanze vietate per doping

Modalità e tempo di conservazione della ricetta

Data limite di utilizzo della preparazione

Uso
□ UI □ UE

Forma farmaceutica

Controllo di qualità obbligatori per le NBP:

Attività terapeutica della preparazione

n°.....li.....Dott.....	
.....	
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Avvertenze.....	
.....	
.....	
Precauzioni.....	
.....	
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Posologia.....	
.....	
.....	
Data limite di utilizzo	
Sig.....	

Costo del contenitore (vaso in plastica con tappo a vite) **0,70 €**

INDICAZIONI DI PERICOLO

Zinco ossido

H400 – molto tossico per gli organismi acquatici

H410 - molto tossico per gli organismi acquatici con effetti di lunga durata

SCADENZA MATERIE PRIME UTILIZZATE: 23 novembre 2021