UNIVERSITÀ DEGLI STUDI DI TORINO

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

SECONDA SESSIONE 2019

PROVA SCRITTA

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- dispensazione dei medicinali
- adempimenti del farmacista

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SECONDA SESSIONE 2019

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 (Ph. Eur. 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.

N.B. Insieme alla prova al candidato vengono fornite copia della monografia ufficiale dei farmaci in questione e copia delle reazioni di identificazione riportate in Ph. Eur. 9.

Riconoscimento del farmaco: *primo riconoscimento*

Il farmaco in esame si presenta come un solido bianco, solubilissimo in acqua; il pH della soluzione acquosa è neutro.

Se si effettua il saggio alla fiamma, si osserva una fiamma giallo-arancione molto intensa.

In base alle caratteristiche sopra riportate sono stati individuati tra i farmaci presenti in Farmacopea due possibili candidati: **sodio cloruro (NaCl)** e **sodio bromuro (NaBr).**

Successivamente si verifica che il farmaco in questione è solubile in etanolo

Indicare quale dei due candidati meglio corrisponde al profilo sperimentale fornito; motivare brevemente tale scelta e proporre almeno ulteriori prove sperimentali per validare la scelta effettuata.

Riconoscimento del farmaco: *secondo riconoscimento*

Il farmaco in esame si presenta come una polvere bianca, con una buona solubilità in acqua che migliora in ambiente acido (HCl 0.5 M), mentre si riduce notevolmente in ambiente basico (NaOH 0.5 M).

In termini di reattività il farmaco in soluzione acquosa trattata con $AgNO_3$, dà origine ad un precipitato bianco.

In base alle caratteristiche sopra riportate sono stati individuati tra i farmaci presenti in Farmacopea due possibili candidati: **procaina cloridrato** e **chinidina solfato.**

Successivamente si verifica che:

1. la soluzione acquosa del farmaco in esame, acidificata con HCl e trattata con una soluzione di bario cloruro ($BaCl_2$), origina un precipitato bianco ed insolubile;
2. la soluzione acquosa del farmaco (circa 1 mg/mL) trattata con acqua di Bromo R ed ammoniaca diluita, sviluppa una colorazione verde.

Indicare quale farmaco corrisponde al profilo sperimentale fornito motivando tale scelta e proporre almeno due ulteriori prove sperimentali per validare la scelta effettuata.

04/2015:0190

SODIUM BROMIDE

Natrii bromidum

NaBr M_r 102.9
[7647-15-6]

DEFINITION

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

CHARACTERS

Appearance: white or almost white, granular powder or small, colourless, transparent or opaque crystals, slightly hygroscopic.

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

IDENTIFICATION

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

B. Solution S (see Tests) gives the reactions of sodium (*2.3.1*).

TESTS

Solution S. Dissolve 10.0 g in *carbon dioxide-free water R* and dilute to 100 mL with the same solvent.

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

Acidity or alkalinity. To 10 mL of solution S add 0.1 mL of *bromothymol blue solution R1*. Not more than 0.5 mL of *0.01 M hydrochloric acid* or *0.01 M sodium hydroxide* is required to change the colour of the indicator.

Bromates. To 10 mL of solution S add 1 mL of *starch solution R*, 0.1 mL of a 100 g/L solution of *potassium iodide R* and 0.25 mL of *0.5 M sulfuric acid* and allow to stand protected from light for 5 min. No blue or violet colour develops.

Chlorides and sulfates. Liquid chromatography (*2.2.29*).

Test solution (a). Dissolve 0.400 g of the substance to be examined in 50 mL of *water for chromatography R* and dilute to 100.0 mL with the same solvent.

Test solution (b). Dilute 25.0 mL of test solution (a) to 50.0 mL with *water for chromatography R*.

Reference solution (a). To 25.0 mL of test solution (a) add 1.0 mL of *sulfate standard solution (10 ppm SO_4) R* and 12.0 mL of *chloride standard solution (50 ppm Cl) R* and dilute to 50.0 mL with *water for chromatography R*.

Reference solution (b). Dilute 10.0 mL of test solution (a) to 100.0 mL with *water for chromatography R*. To 2.0 mL of this solution add 8.0 mL of *chloride standard solution (50 ppm Cl) R* and dilute to 20.0 mL with *water for chromatography R*.

Blank solution: *water for chromatography R*.

Column:

- *size*: l = 0.25 m, Ø = 2 mm;
- *stationary phase*: *strongly basic anion-exchange resin for chromatography R* (13 µm).

Mobile phase: dissolve 0.600 g of *potassium hydroxide R* in *water for chromatography R* and dilute to 1000.0 mL with the same solvent.

Flow rate: 0.4 mL/min.

Detection: conductivity detector equipped with a suitable ion suppressor.

Injection: 50 µL of test solution (b), reference solutions (a) and (b) and the blank solution.

Run time: 2.5 times the retention time of bromide.

Retention time: chloride = about 5 min; bromide = about 8 min; sulfate = about 16 min.

System suitability: reference solution (b):

- *resolution*: minimum 8.0 between the peaks due to chloride and bromide.

Calculation of percentage contents:

- for chlorides, use the concentration of chloride in reference solution (a); correct the area of the peak due to chloride in the chromatogram obtained with reference solution (a) by subtracting the area of the peak due to chloride in the chromatogram obtained with test solution (b);
- for sulfates, use the concentration of sulfate in reference solution (a); correct the area of the peak due to sulfate in the chromatogram obtained with reference solution (a) by subtracting the area of the peak due to sulfate in the chromatogram obtained with test solution (b).

Limits:

- *chlorides*: maximum 0.6 per cent;
- *sulfates*: maximum 0.01 per cent.

Iodides. To 5 mL of solution S add 0.15 mL of *ferric chloride solution R1* and 2 mL of *methylene chloride R*. Shake and allow to separate. The lower layer is colourless (*2.2.2, Method I*).

Iron (*2.4.9*): maximum 20 ppm.

Dilute 5 mL of solution S to 10 mL with *water R*.

Magnesium and alkaline-earth metals (*2.4.7*): maximum 200 ppm, calculated as Ca.

10.0 g complies with the test for magnesium and alkaline-earth metals. The volume of *0.01 M sodium edetate* used does not exceed 5.0 mL.

Heavy metals (*2.4.8*): maximum 10 ppm.

12 mL of solution S complies with test A. Prepare the reference solution using *lead standard solution (1 ppm Pb) R*.

Loss on drying (*2.2.32*): maximum 3.0 per cent, determined on 1.000 g by drying in an oven at 105 °C for 3 h.

ASSAY

Dissolve 85.0 mg in *water R*, add 5 mL of *dilute nitric acid R* and dilute to 50 mL with *water R*. Titrate with *0.1 M silver nitrate*, determining the end-point potentiometrically (*2.2.20*).

1 mL of *0.1 M silver nitrate* is equivalent to 10.29 mg of NaBr.

Calculate the percentage content of NaBr using the following expression:

$$a - 2.902\,b$$

a = percentage content of NaBr and NaCl obtained in the assay and calculated as NaBr;

b = percentage content of Cl obtained in the test for chlorides.

STORAGE

In an airtight container.

04/2015:0193

SODIUM CHLORIDE(1)

Natrii chloridum

NaCl M_r 58.44
[7647-14-5]

DEFINITION

Content: 99.0 per cent to 100.5 per cent (dried substance).

♦CHARACTERS

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

(1) This monograph has undergone pharmacopoeial harmonisation. See chapter *5.8. Pharmacopoeial harmonisation*.

Solubility: freely soluble in water, practically insoluble in anhydrous ethanol. ♦

IDENTIFICATION

A. It gives reaction (a) of chlorides (*2.3.1*).

B. It gives the reactions of sodium (*2.3.1*).

TESTS

◊*If the substance is in the form of pearls, crush before use.*◊

Solution S. Dissolve 20.0 g in *carbon dioxide-free water R* prepared from *distilled water R* and dilute to 100.0 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 20 mL of solution S add 0.1 mL of *bromothymol blue solution R1*. Not more than 0.5 mL of *0.01 M hydrochloric acid* or *0.01 M sodium hydroxide* is required to change the colour of the indicator.

Bromides: maximum 100 ppm.

To 0.5 mL of solution S add 4.0 mL of *water R*, 2.0 mL of *phenol red solution R2* and 1.0 mL of a 0.1 g/L solution of *chloramine R* and mix immediately. After exactly 2 min, add 0.15 mL of *0.1 M sodium thiosulfate*, mix and dilute to 10.0 mL with *water R*. The absorbance (*2.2.25*) of the solution measured at 590 nm, using *water R* as the compensation liquid, is not greater than that of a standard prepared at the same time and in the same manner, using 5.0 mL of a 3.0 mg/L solution of *potassium bromide R*.

Ferrocyanides. Dissolve 2.0 g in 6 mL of *water R*. Add 0.5 mL of a mixture of 5 mL of a 10 g/L solution of *ferric ammonium sulfate R* in a 2.5 g/L solution of *sulfuric acid R* and 95 mL of a 10 g/L solution of *ferrous sulfate R*. No blue colour develops within 10 min.

Iodides. Moisten 5 g by the dropwise addition of a freshly prepared mixture of 0.15 mL of *sodium nitrite solution R*, 2 mL of *0.5 M sulfuric acid*, 25 mL of *iodide-free starch solution R* and 25 mL of *water R*. After 5 min, examine in daylight. The mixture shows no blue colour.

Nitrites. To 10 mL of solution S add 10 mL of *water R*. The absorbance (*2.2.25*) is not greater than 0.01 at 354 nm.

Phosphates (*2.4.11*): maximum 25 ppm.

Dilute 2 mL of solution S to 100 mL with *water R*.

Sulfates (*2.4.13*): maximum 200 ppm.

Dilute 7.5 mL of solution S to 30 mL with *distilled water R*.

Aluminium (*2.4.17*): maximum 0.2 ppm, if intended for use in the manufacture of peritoneal dialysis solutions, haemodialysis solutions or haemofiltration solutions.

Prescribed solution. Dissolve 20.0 g in 100 mL of *water R* and add 10 mL of *acetate buffer solution pH 6.0 R*.

Reference solution. Mix 2 mL of *aluminium standard solution (2 ppm Al) R*, 10 mL of *acetate buffer solution pH 6.0 R* and 98 mL of *water R*.

Blank solution. Mix 10 mL of *acetate buffer solution pH 6.0 R* and 100 mL of *water R*.

♦**Arsenic** (*2.4.2, Method A*): maximum 1 ppm, determined on 5 mL of solution S. ♦

Barium. To 5 mL of solution S add 5 mL of *distilled water R* and 2 mL of *dilute sulfuric acid R*. After 2 h, any opalescence in the solution is not more intense than that in a mixture of 5 mL of solution S and 7 mL of *distilled water R*.

Iron (*2.4.9*): maximum 2 ppm, determined on solution S.

Prepare the standard using a mixture of 4 mL of *iron standard solution (1 ppm Fe) R* and 6 mL of *water R*.

Magnesium and alkaline-earth metals (*2.4.7*): maximum 100 ppm, calculated as Ca and determined on 10.0 g.

Use 0.150 g of *mordant black 11 triturate R*. The volume of *0.01 M sodium edetate* used is not more than 2.5 mL.

Potassium: maximum 500 ppm, if intended for use in the manufacture of parenteral preparations or haemodialysis, haemofiltration or peritoneal dialysis solutions.

Atomic emission spectrometry (*2.2.22, Method I*).

Test solution. Dissolve 1.00 g in *water R* and dilute to 100.0 mL with the same solvent.

Reference solutions. Dissolve 1.144 g of *potassium chloride R*, previously dried at 100-105 °C for 3 h, in *water R* and dilute to 1000.0 mL with the same solvent (600 µg of K per millilitre). Dilute as required.

Wavelength: 766.5 nm.

♦**Heavy metals** (*2.4.8*): maximum 5 ppm.

12 mL of solution S complies with test A. Prepare the reference solution using *lead standard solution (1 ppm Pb) R*. ♦

Loss on drying (*2.2.32*): maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C for 2 h.

♦**Bacterial endotoxins** (*2.6.14*): less than 5 IU/g, if intended for use in the manufacture of parenteral preparations without a further appropriate procedure for removal of bacterial endotoxins. ♦

ASSAY

Dissolve 50.0 mg in *water R* and dilute to 50 mL with the same solvent. Titrate with *0.1 M silver nitrate* determining the end-point potentiometrically (*2.2.20*).

1 mL of *0.1 M silver nitrate* is equivalent to 5.844 mg of NaCl.

♦LABELLING

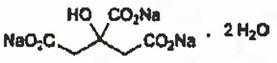
The label states:

- where applicable, that the substance is suitable for use in the manufacture of parenteral preparations;
- where applicable, that the substance is suitable for use in the manufacture of peritoneal dialysis solutions, haemodialysis solutions or haemofiltration solutions. ♦

04/2015:0412

SODIUM CITRATE

Natrii citras



$C_6H_5Na_3O_7,2H_2O$ M_r 294.1

[6132-04-3]

DEFINITION

Trisodium 2-hydroxypropane-1,2,3-tricarboxylate dihydrate.

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

CHARACTERS

Appearance: white or almost white, crystalline powder or white or almost white, granular crystals, slightly deliquescent in moist air.

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

IDENTIFICATION

A. To 1 mL of solution S (see Tests) add 4 mL of *water R*. The solution gives the reaction of citrates (*2.3.1*).

B. 1 mL of solution S gives reaction (a) of sodium (*2.3.1*).

E. Dilute 1 mL of solution S (see Tests) to 2 mL with *water R*. 1 mL of this solution gives the reaction of primary aromatic amines (*2.3.1*).

TESTS

Solution S. Dissolve 2.5 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_6 (*2.2.2, Method II*).

pH (*2.2.3*). The pH of solution S is 5.6 to 6.3.

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

Test solution. Dissolve 0.10 g of the substance to be examined in *alcohol R* and dilute to 10 mL with the same solvent.

Reference solution. Dilute 1 mL of the test solution to 200 mL with *alcohol R*.

Apply to the plate 5 µL of each solution. Develop over a path of 12 cm using a mixture of 15 volumes of *glacial acetic acid R*, 30 volumes of *water R* and 60 volumes of *butanol R*. Place the plate in a stream of cold air until the plate appears dry. Examine in ultraviolet light at 254 nm. Any spot in the chromatogram obtained with the test solution, apart from the principal spot, is not more intense than the spot in the chromatogram obtained with the reference solution (0.5 per cent).

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

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

ASSAY

Dissolve 0.2500 g in 50 mL of *dilute hydrochloric acid R*. Carry out the determination of primary aromatic amino-nitrogen (*2.5.8*).

1 mL of *0.1 M sodium nitrite* is equivalent to 27.18 mg of $C_{13}H_{22}ClN_3O$.

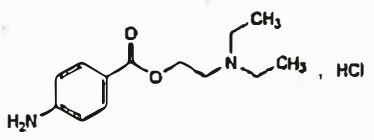
STORAGE

Store in an airtight container, protected from light.

01/2017:0050

PROCAINE HYDROCHLORIDE

Procaini hydrochloridum



$C_{13}H_{21}ClN_2O_2$ M_r 272.8
[51-05-8]

DEFINITION

Procaine hydrochloride contains not less than 99.0 per cent and not more than the equivalent of 101.0 per cent of 2-(diethylamino)ethyl 4-aminobenzoate hydrochloride, calculated with reference to the dried substance.

CHARACTERS

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

IDENTIFICATION

First identification: A, B, E.

Second identification: A, C, D, E, F.

A. Melting point (*2.2.14*): 154 °C to 158 °C.

B. Examine by infrared absorption spectrophotometry (*2.2.24*), comparing with the spectrum obtained with *procaine hydrochloride CRS*.

C. To about 5 mg add 0.5 mL of *fuming nitric acid R*. Evaporate to dryness on a water-bath, allow to cool and dissolve the residue in 5 mL of *acetone R*. Add 1 mL of *0.1 M alcoholic potassium hydroxide*. Only a brownish-red colour develops.

D. To 0.2 mL of solution S (see Tests) add 2 mL of *water R* and 0.5 mL of *dilute sulfuric acid R* and shake. Add 1 mL of a 1 g/L solution of *potassium permanganate R*. The colour is immediately discharged.

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

F. Dilute 1 mL of solution S to 100 mL with *water R*. 2 mL of this solution gives the reaction of primary aromatic amines (*2.3.1*).

TESTS

Solution S. Dissolve 2.5 g in *carbon dioxide-free water R* and dilute to 50 mL with the same solvent.

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

pH (*2.2.3*). Dilute 4 mL of solution S to 10 mL with *carbon dioxide-free water R*. The pH of the solution is 5.0 to 6.5.

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

Test solution. Dissolve 1.0 g of the substance to be examined in *water R* and dilute to 10 mL with the same solvent.

Reference solution. Dissolve 50 mg of *4-aminobenzoic acid R* in *water R* and dilute to 100 mL with the same solvent. Dilute 1 mL of the solution to 10 mL with *water R*.

Apply separately to the plate 5 µL of each solution. Develop over a path of 10 cm using a mixture of 4 volumes of *glacial acetic acid R*, 16 volumes of *hexane R* and 80 volumes of *dibutyl ether R*. Dry the plate at 100 °C to 105 °C for 10 min and examine in ultraviolet light at 254 nm. Any spot in the chromatogram obtained with the test solution, apart from the principal spot, is not more intense than the spot in the chromatogram obtained with the reference solution (0.05 per cent). The principal spot in the chromatogram obtained with the test solution remains on the point of application.

Loss on drying (*2.2.32*). Not more than 0.5 per cent, determined on 1.00 g by drying in an oven at 105 °C.

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

ASSAY

Dissolve 0.400 g in 50 mL of *dilute hydrochloric acid R*. Carry out the determination of primary aromatic amino nitrogen (*2.5.8*).

1 mL of *0.1 M sodium nitrite* is equivalent to 27.28 mg of $C_{13}H_{21}ClN_2O_2$.

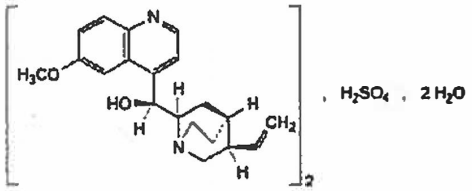
STORAGE

Store protected from light.

01/2016:0017

QUINIDINE SULFATE

Chinidini sulfas



$C_{40}H_{50}N_4O_8S,2H_2O$ M_r 783
[6591-63-5]

DEFINITION

Alkaloid monosulfates, expressed as bis[(*S*)-[(2*R*,4*S*,5*R*)-5-ethenyl-1-azabicyclo[2.2.2]oct-2-yl](6-methoxyquinolin-4-yl)methanol] sulfate dihydrate.

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

CHARACTERS

Appearance: white or almost white, crystalline powder or silky, colourless needles.

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

IDENTIFICATION

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

Test solution. Dissolve 0.10 g of the substance to be examined in *methanol R* and dilute to 10 mL with the same solvent.

Reference solution. Dissolve 0.10 g of *quinidine sulfate CRS* in *methanol R* and dilute to 10 mL with the same solvent.

Plate: *TLC silica gel G plate R.*

Mobile phase: *diethylamine R, ether R, toluene R* (10:24:40 *V/V/V*).

Application: 5 µL.

Development: twice over a path of 15 cm; dry in a current of air for 15 min between the 2 developments.

Drying: at 105 °C for 30 min and allow to cool.

Detection: spray with *iodoplatinate reagent R.*

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

B. Dissolve about 5 mg in 5 mL of *water R*. Add 0.2 mL of *bromine water R* and 1 mL of *dilute ammonia R2*. A green colour develops.

C. Dissolve 0.1 g in 3 mL of *dilute sulfuric acid R* and dilute to 100 mL with *water R*. When examined in ultraviolet light at 366 nm, an intense blue fluorescence appears which disappears almost completely on addition of 1 mL of *hydrochloric acid R*.

D. Dissolve about 50 mg in 5 mL of hot *water R*, cool, add 1 mL of *silver nitrate solution R1* and stir with a glass rod. After a few minutes, a white precipitate is formed that dissolves on the addition of *dilute nitric acid R*.

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

F. pH (see Tests).

TESTS

Solution S. Dissolve 0.500 g in *0.1 M hydrochloric acid* and dilute to 25.0 mL with the same acid.

Appearance of solution. Solution S is clear (*2.2.1*) and not more intensely coloured than reference solution GY_6 (*2.2.2, Method II*).

pH (*2.2.3*): 6.0 to 6.8.

Dissolve 0.10 g in *carbon dioxide-free water R* and dilute to 10 mL with the same solvent.

Specific optical rotation (*2.2.7*): + 275 to + 290 (dried substance), determined on solution S.

Other cinchona alkaloids. Liquid chromatography (*2.2.29*): use the normalisation procedure.

Test solution. Dissolve 20 mg of the substance to be examined in 5 mL of the mobile phase, with gentle heating if necessary, and dilute to 10 mL with the mobile phase.

Reference solution (a). Dissolve 20 mg of *quinine sulfate CRS* (impurity A) in 5 mL of the mobile phase, with gentle heating if necessary, and dilute to 10 mL with the mobile phase.

Reference solution (b). Dissolve 20 mg of *quinidine sulfate CRS* in 5 mL of the mobile phase, with gentle heating if necessary, and dilute to 10 mL with the mobile phase.

Reference solution (c). To 1 mL of reference solution (a) add 1 mL of reference solution (b).

Reference solution (d). Dilute 1.0 mL of reference solution (a) to 10.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 50.0 mL with the mobile phase.

Reference solution (e). Dissolve 10 mg of *thiourea R* in the mobile phase and dilute to 10 mL with the mobile phase.

Column:

- *size*: *l* = 0.15-0.25 m, Ø = 4.6 mm;
- *stationary phase*: *octadecylsilyl silica gel for chromatography R* (5-10 µm).

Mobile phase: dissolve 6.8 g of *potassium dihydrogen phosphate R* and 3.0 g of *hexylamine R* in 700 mL of *water R*, adjust to pH 2.8 with *dilute phosphoric acid R*, add 60 mL of *acetonitrile R* and dilute to 1000 mL with *water R*.

Flow rate: 1.5 mL/min.

Detection: spectrophotometer at 250 nm for reference solution (c) and at 316 nm for the other solutions.

Injection: 10 µL.

Run time: 2.5 times the retention time of quinidine.

Identification of peaks: use the chromatogram obtained with reference solution (a) to identify the peaks due to impurity A and dihydroquinine; use the chromatogram obtained with reference solution (b) to identify the peaks due to quinidine and impurity C; the chromatogram obtained with reference solution (c) shows 4 peaks due to quinidine, impurity A, impurity C and dihydroquinine which are identified by comparison of their retention times with those of the corresponding peaks in the chromatograms obtained with reference solutions (a) and (b).

Relative retention with reference to impurity A: dihydroquinine = about 1.4.

Relative retention with reference to quinidine: impurity C = about 1.5.

System suitability:

- *resolution*: minimum 3.0 between the peaks due to impurity A and quinidine and minimum 2.0 between the peaks due to impurities C and A in the chromatogram obtained with reference solution (c);
- *signal-to-noise ratio*: minimum 4 for the principal peak in the chromatogram obtained with reference solution (d);
- *mass distribution ratio*: 3.5 to 4.5 for the peak due to quinidine in the chromatogram obtained with reference solution (b), t_R being calculated from the peak due to thiourea in the chromatogram obtained with reference solution (e); if necessary, adjust the concentration of acetonitrile in the mobile phase.

Limits:

- *impurity C*: maximum 15 per cent;
- *any impurity eluted before quinidine*: for each impurity, maximum 5 per cent;

Monographs Z-Q

- *any other impurity*: for each impurity, maximum 2.5 per cent;
- *disregard limit*: the area of the principal peak in the chromatogram obtained with reference solution (d) (0.2 per cent).

Boron: maximum 5 ppm. *Avoid where possible the use of glassware.*

Test solution. Dissolve 1.00 g in a mixture of 0.5 mL of *hydrochloric acid R* and 4.0 mL of *water R*.

Reference solution. Dissolve 0.572 g of *boric acid R* in *water R* and dilute to 1000.0 mL with the same solvent. Dilute 5.0 mL of the solution to 100.0 mL with *water R*. To 1.0 mL of this solution add 3.0 mL of *water R* and 0.5 mL of *hydrochloric acid R*.

Blank solution. Add 0.5 mL of *hydrochloric acid R* to 4.0 mL of *water R*.

Add 3.0 mL of a 100 g/L solution of *2-ethylhexane-1,3-diol R* in *methylene chloride R* to the test solution, to the reference solution and to the blank solution, then shake for 1 min. Allow to stand for 6 min. To 1.0 mL of the lower layer, add 2.0 mL of a 3.75 g/L solution of *curcumin R* in *anhydrous acetic acid R* and 0.3 mL of *sulfuric acid R*. Mix and after 20 min add 25.0 mL of *ethanol (96 per cent) R*. Mix. The blank solution is yellow. Any red colour in the test solution is not more intense than that in the reference solution.

Loss on drying (*2.2.32*): 3.0 per cent to 5.0 per cent, determined on 1.000 g by drying in an oven at 130 °C.

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

ASSAY

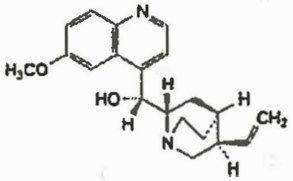
Dissolve 0.200 g in 20 mL of *acetic anhydride R*. Titrate with *0.1 M perchloric acid*, using 0.15 mL of *naphtholbenzein solution R* as indicator.

1 mL of *0.1 M perchloric acid* is equivalent to 24.90 mg of $C_{40}H_{50}N_4O_8S$.

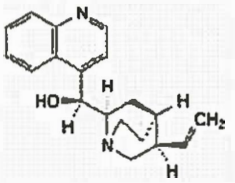
STORAGE

Protected from light.

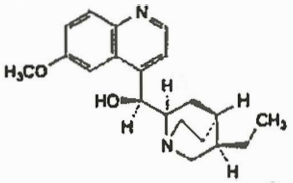
IMPURITIES



A. (*R*)-[(2*S*,4*S*,5*R*)-5-ethenyl-1-azabicyclo[2.2.2]oct-2-yl](6-methoxyquinolin-4-yl)methanol (quinine),



B. (*S*)-[(2*R*,4*S*,5*R*)-5-ethenyl-1-azabicyclo[2.2.2]oct-2-yl](quinolin-4-yl)methanol (cinchonine),

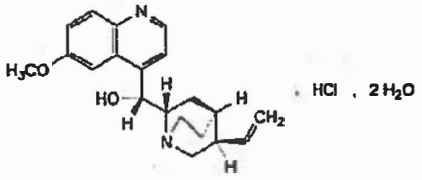


C. (*S*)-[(2*R*,4*S*,5*R*)-5-ethyl-1-azabicyclo[2.2.2]oct-2-yl](6-methoxyquinolin-4-yl)methanol (dihydroquinidine).

01/2016:0018

QUININE HYDROCHLORIDE

Chinini hydrochloridum



$C_{20}H_{25}ClN_2O_2,2H_2O$ M_r 396.9

[6119-47-7]

DEFINITION

Alkaloid monohydrochlorides, expressed as (*R*)-[(2*S*,4*S*,5*R*)-5-ethenyl-1-azabicyclo[2.2.2]oct-2-yl](6-methoxyquinolin-4-yl)methanol hydrochloride dihydrate.

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

CHARACTERS

Appearance: white or almost white or colourless, fine, silky needles, often in clusters.

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

IDENTIFICATION

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

Test solution. Dissolve 0.10 g of the substance to be examined in *methanol R* and dilute to 10 mL with the same solvent.

Reference solution. Dissolve 0.10 g of *quinine sulfate CRS* in *methanol R* and dilute to 10 mL with the same solvent.

Plate: *TLC silica gel G plate R.*

Mobile phase: *diethylamine R, ether R, toluene R* (10:24:40 *V/V/V*).

Application: 5 µL.

Development: twice over a path of 15 cm; dry in a current of air for 15 min between the 2 developments.

Drying: at 105 °C for 30 min and allow to cool.

Detection: spray with *iodoplatinate reagent R.*

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

B. Dissolve about 10 mg in *water R* and dilute to 10 mL with the same solvent. To 5 mL of this solution add 0.2 mL of *bromine water R* and 1 mL of *dilute ammonia R2*. A green colour develops.

C. Dissolve 0.1 g in 3 mL of *dilute sulfuric acid R* and dilute to 100 mL with *water R*. When examined in ultraviolet light at 366 nm, an intense blue fluorescence appears which disappears almost completely on the addition of 1 mL of *hydrochloric acid R*.

D. It gives the reactions of chlorides (*2.3.1*).

E. pH (see Tests).

TESTS

Solution S. Dissolve 1.0 g in *carbon dioxide-free water R* prepared from *distilled water R* and dilute to 50 mL with the same solvent.

Appearance of solution. Solution S is clear (*2.2.1*) and not more intensely coloured than reference solution Y_6 (*2.2.2, Method II*).

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 2019

PROVA PRATICA: Dosamento del Farmaco

Cognome e nome.....

L'acido tartarico è presente come eccipiente nelle bustine di un granulato effervescente.
Dovendo dosare l'acido tartarico contenuto in ciascuna bustina, si esegue una titolazione come da monografia di Farmacopea Europea 9.

A tale scopo, il contenuto di 10 bustine del peso complessivo di 50,836 g è stato trasferito in matraccio da 100 mL e dopo aver portato a volume con acqua si è ottenuta la soluzione A. Successivamente 25 mL di soluzione A sono stati prelevati e titolati secondo Ph. Eur. 9; la titolazione ha richiesto 15.75 mL di sodio idrossido 1,000 M.

Si calcolino:

a) i grammi di acido tartarico in ogni bustina;

b) la % in peso di acido tartarico in ogni bustina;

c) la concentrazione molare (M) e la concentrazione normale (N) della soluzione A.

Considerato che ogni bustina dovrebbe contenere 0,4650 g di eccipiente con una variabilità di ± 5%:

d) si determini l'intervallo di peso dell'acido tartarico che deve essere contenuto in ogni bustina perché questa sia considerata conforme alle specifiche;

e) si dichiari se le bustine in questione siano da considerarsi conformi alle specifiche.

Risposte ai quesiti:

a) _____

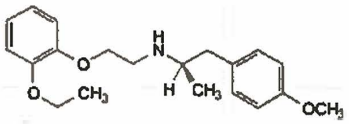
b) _____

c) _____

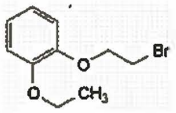
d) _____

e) _____

N.B. Insieme alla prova al candidato viene fornita copia della monografia ufficiale di Ph. Eur. 9 di acido tartarico.



H. (2*R*)-*N*-[2-(2-ethoxyphenoxy)ethyl]-1-(4-methoxyphenyl)-propan-2-amine,



I. 1-(2-bromoethoxy)-2-ethoxybenzene.

01/2008:1477
corrected 6.0

TANNIC ACID

Tannin̲um

DEFINITION

Mixture of esters of glucose with gallic acid and 3-galloylgallic acid.

CHARACTERS

Appearance: yellowish-white or slightly brown amorphous light powder or shiny plates.

Solubility: very soluble in water, freely soluble in acetone, in ethanol (96 per cent) and in glycerol (85 per cent), practically insoluble in methylene chloride.

IDENTIFICATION

A. Dilute 0.1 mL of solution S (see Tests) to 5 mL with *water R*. Add 0.1 mL of *ferric chloride solution R1*. A blackish-blue colour is produced which becomes green on the addition of 1 mL of *dilute sulfuric acid R*.

B. To 1 mL of solution S, add 3 mL of a 1 g/L solution of *gelatin R*. The mixture becomes turbid and a flocculent precipitate is formed.

C. Dilute 0.1 mL of solution S to 5 mL with *water R*. Add 0.3 mL of *barium hydroxide solution R*. A greenish-blue precipitate is formed.

TESTS

Solution S. Dissolve 4.0 g in *carbon dioxide-free water R* and dilute to 20 mL with the same solvent.

Appearance of solution. Solution S is not more opalescent than reference suspension II (*2.2.1*).

Dextrins, gum, salts, sugars. To 2 mL of solution S, add 2 mL of *ethanol (96 per cent) R*. The solution is clear. Add 1 mL of *ether R*. The solution remains clear for at least 10 min.

Resins. To 5 mL of solution S, add 5 mL of *water R*. The mixture remains clear (*2.2.1*) for at least 15 min.

Loss on drying (*2.2.32*): maximum 12.0 per cent, determined on 0.200 g by drying at 105 °C.

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

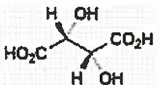
STORAGE

Protected from light.

01/2017:0460

TARTARIC ACID

Acidum tartaricum



$C_4H_6O_6$ M_r 150.1
[87-69-4]

DEFINITION

(2*R*,3*R*)-2,3-Dihydroxybutanedioic acid.

The substance is of natural origin, obtained by extraction of lees during winemaking.

Content: 99.5 per cent to 101.0 per cent (dried substance).

CHARACTERS

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

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

IDENTIFICATION

A. Solution S (see Tests) is strongly acid (*2.2.4*).

B. It gives the reactions of tartrates (*2.3.1*).

TESTS

Solution S. Dissolve 5.0 g in *distilled water R* and dilute to 50 mL with the same solvent.

Appearance of solution. Solution S is clear (*2.2.1*) and not more intensely coloured than reference solution Y_6 (*2.2.2, Method II*).

Specific optical rotation (*2.2.7*): + 12.0 to + 12.8 (dried substance).

Dissolve 5.00 g in *water R* and dilute to 25.0 mL with the same solvent.

Oxalic acid: maximum 360 ppm, calculated as anhydrous oxalic acid.

Dissolve 0.80 g in 4 mL of *water R*. Add 3 mL of *hydrochloric acid R* and 1 g of *zinc R* in granules and boil for 1 min. Allow to stand for 2 min. Collect the liquid in a test-tube containing 0.25 mL of a 10 g/L solution of *phenylhydrazine hydrochloride R* and heat to boiling. Cool rapidly, transfer to a graduated cylinder and add an equal volume of *hydrochloric acid R* and 0.25 mL of a 50 g/L solution of *potassium ferricyanide R*. Shake and allow to stand for 30 min. Any pink colour in the solution is not more intense than that in a standard prepared at the same time in the same manner using 4 mL of a 0.1 g/L solution of *oxalic acid R*.

Chlorides (*2.4.4*): maximum 100 ppm.

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

Sulfates (*2.4.13*): maximum 150 ppm.

Dilute 10 mL of solution S to 15 mL with *distilled water R*.

Calcium (*2.4.3*): maximum 200 ppm.

To 5 mL of solution S add 10 mL of a 50 g/L solution of *sodium acetate R* in *distilled water R*.

Loss on drying (*2.2.32*): maximum 0.2 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

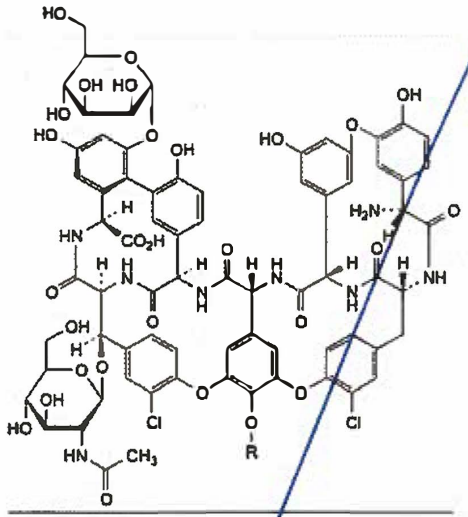
Dissolve 0.650 g in 25 mL of *water R*. Titrate with *1 M sodium hydroxide* using 0.5 mL of *phenolphthalein solution R* as indicator, until a pink colour is obtained.

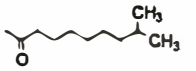
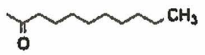
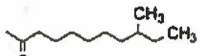
1 mL of *1 M sodium hydroxide* is equivalent to 75.05 mg of $C_4H_6O_6$.

01/2017:2358

TEICOPLANIN

Teicoplaninum



Teicoplanin	R	R'
$A_{2\text{-}1}$ $C_{88}H_{95}Cl_2N_9O_{33}$ M. W.: 1878	H	
$A_{2\text{-}2}$ $C_{88}H_{97}Cl_2N_9O_{33}$ M. W.: 1880	H	
$A_{2\text{-}3}$ $C_{88}H_{97}Cl_2N_9O_{33}$ M. W.: 1880	H	
$A_{2\text{-}4}$ $C_{89}H_{99}Cl_2N_9O_{33}$ M. W.: 1894	H	
$A_{2\text{-}5}$ $C_{89}H_{99}Cl_2N_9O_{33}$ M. W.: 1894	H	
$A_{3\text{-}1}$ $C_{72}H_{68}Cl_2N_8O_{28}$ M. W.: 1564	H	

DEFINITION

Mixture of glycopeptides produced by certain strains of *Actinoplanes teichomyceticus sp.*; the 6 principal components of the mixture are teicoplanin $A_{2\text{-}1}$ to $A_{2\text{-}5}$ and teicoplanin $A_{3\text{-}1}$.

Fermentation product.

Potency: minimum 900 IU/mg (anhydrous and sodium chloride-free substance).

CHARACTERS

Appearance: yellowish, amorphous powder.

Solubility: freely soluble in water, sparingly soluble in dimethylformamide, practically insoluble in ethanol (96 per cent *V/V*).

IDENTIFICATION

A. Infrared absorption spectrophotometry (*2.2.24*).

Comparison: *teicoplanin for identification CRS*.

B. Examine the chromatograms obtained in the test for composition and related substances.

Results: the principal peaks (teicoplanins $A_{3\text{-}1}$, $A_{2\text{-}1}$, $A_{2\text{-}2}$, $A_{2\text{-}3}$, $A_{2\text{-}4}$ and $A_{2\text{-}5}$) in the chromatogram obtained with the test solution are similar in retention time and size to the principal peaks in the chromatogram obtained with reference solution (a).

TESTS

Appearance of solution. The solution is clear (*2.2.1*) and not more intensely coloured than reference solution BY_3 or B_4 (*2.2.2, Method I*).

Dissolve 0.8 g in 10 mL of *water R*.

pH (*2.2.3*): 6.5 to 7.5.

Dissolve 0.50 g in *carbon dioxide-free water R* and dilute to 10 mL with the same solvent.

Composition and related substances. Liquid chromatography (*2.2.29*): use the normalisation procedure.

Test solution. Dissolve 0.100 g of the substance to be examined in *water R* and dilute to 50.0 mL with the same solvent.

Reference solution (a). Dissolve 20 mg of *teicoplanin for identification CRS* in *water R* and dilute to 10.0 mL with the same solvent.

Reference solution (b). Dilute 1.0 mL of reference solution (a) to 10.0 mL with *water R*. Dilute 1.0 mL of this solution to 20.0 mL with *water R*.

Reference solution (c). Dissolve 50.0 mg of *mesityl oxide CRS* in *water R* and dilute to 25.0 mL with the same solvent. Dilute 1.0 mL of the solution to 10.0 mL with *water R*. Dilute 1.0 mL of this solution to 100.0 mL with *water R*.

Column:

- *size*: *l* = 0.25 m, Ø = 4.6 mm;
- *stationary phase*: spherical *end-capped octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase:

- *mobile phase A*: mix 900 mL of a 3.0 g/L solution of *anhydrous sodium dihydrogen phosphate R*, adjusted to pH 6.0 with *1 M sodium hydroxide*, and 100 mL of *acetonitrile R*;
- *mobile phase B*: mix 300 mL of a 3.0 g/L solution of *anhydrous sodium dihydrogen phosphate R*, adjusted to pH 6.0 with *1 M sodium hydroxide*, and 700 mL of *acetonitrile R*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 30	100 → 50	0 → 50
30 - 31	50 → 10	50 → 90
31 - 35	10	90

Flow rate: 2.3 mL/min.

Detection: spectrophotometer at 254 nm.

Injection: 20 µL.

Identification: use the chromatogram supplied with *teicoplanin for identification CRS* and the chromatogram obtained with reference solution (a) to identify the groups and impurities.

Relative retention of groups and impurities with reference to teicoplanin $A_{2\text{-}2}$:

- teicoplanin A_3 group ≤ 0.70;

Monographs T

1

Dott. XXXXX YYYYY
Via Xxxxx, xx
Torino
Tel. 011.XX.XX.XXX

Sig. XXXXXX YYYYY

R/	Solfo precipitato (magistero)		16	g
	Acido salicilico		4	g
	Paraffina liquida		10	g
	Vaselina bianca	q.b.	100	g

Preparare 80 g

2 applicazioni al dì

20/11/2019

UTILIZZARE IL FOGLIO PROTOCOLLO A QUADRETTI **UNICAMENTE** PER I CALCOLI

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) 0,80 €

INDICAZIONI DI PERICOLO

Acido salicilico

H302 – nocivo se ingerito

H318 – provoca gravi lesioni oculari

Solfo precipitato

H315 – Provoca irritazione cutanea

SCADENZA MATERIE PRIME UTILIZZATE: 19 luglio 2020