EUROPEAN PHARMACOPŒIA

COUNCIL OF EUROPE

2nd EDITION

Part. II - 2

MAISONNEUVE

EUROPEAN PHARMACOPOEIA

SECOND EDITION

Part II

Second Fascicule

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TEXTS INCLUDED IN THE SECOND FASCICULE

Revised Monographs with their Serial Number

Atropini Sulfas (68)	Atropine Sulphate
Chloramphenicolum (71)	Chloramphenicol
Cocaini Hydrochloridum (73)	Cocaine Hydrochloride
Codeini Phosphas Hemihydricus (74)	Codeine Phosphate Hemihydrate
Codeini Phosphas Sesquihydricus (75)	Codeine Phosphate Sesquihydrate
Codeinum (76)	Codeine
Digitoxinum (78)	Digitoxin
Digoxinum (79)	Digoxin
Ergocalciferolum (82)	Ergocalciferol
Ferrosi Sulfas (83)	Ferrous Sulphate
Immunosera ad Usum Humanum (84)	Immunosera for Human Use
Immunoserum Botulinicum (85)	Botulinum Antitoxin
Immunoserum Diphthericum (86)	Diphtheria Antitoxin
Immunoserum Gangraenicum (Clostridium Novyi) (87)	Gas-gangrene Antitoxin (Novyi)
Immunoserum Gangraenicum (Clostridium Perfringens) (88)	Gas-gangrene Antitoxin (Perfringens)
Immunoserum Gangraenicum (Clostridium Septicum) (89)	Gas-gangrene Antitoxin (Septicum)
Immunoserum Gangraenicum Mixtum (90)	Mixed Gas-gangrene Antitoxin
Immunoserum Tetanicum ad Usum Humanum (91)	Tetanus Antitoxin for Human Use
Ipecacuanhae Pulvis Normatus (93)	Prepared Ipecacuanha
Ipecacuanhae Radix (94)	Ipecacuanha Root

Morphini Hydrochloridum (97)	Morphine Hydrochloride
Natrii Sulfas Anhydricus (99)	Anhydrous Sodium Sulphate
Natrii Sulfas Decahydricus (100)	Sodium Sulphate Decahydrate
Papaverini Hydrochloridum (102)	Papaverine Hydrochloride
Pilocarpini Nitras (104)	Pilocarpine Nitrate
Rhamni Purshiani Cortex (105)	Cascara
Scopolamini Hydrobromidum (106)	Hyoscine Hydrobromide
Zinci Chloridum (110)	Zinc Chloride
Zinci Sulfas (111)	Zinc Sulphate

New Monographs with their Serial Number

Acidum Benzoicum (66)	Benzoic Acid
Acidum Folicum (67)	Folic Acid
Cera Alba (69)	White Beeswax
Cera Flava (70)	Yellow Beeswax
Cholecalciferolum (72)	Cholecalciferol
	Cholecalciferol Concentrate (Oily Form)
	Cholecalciferol Concentrate (Powder Form)
Dapsonum (77)	Dapsone
Emetini Hydrochloridum Heptahydricum (80)	Emetine Hydrochloride Heptahydrate
Emetini Hydrochloridum Pentahydricum (81)	Emetine Hydrochloride Pentahydrate
Indometacinum (92)	Indometacin
Lini Semen (95)	Linseed
Mercaptopurinum (96)	Mercaptopurine
Natrii Laurilsulfas (98)	Sodium Lauryl Sulphate
Nitrofurantoinum (101)	Nitrofurantoin
Phenylhydrargyri Boras (103)	Phenylmercuric Borate
Sulfacetamidum Natricum (107)	Sulfacetamide Sodium
Sulfamethoxazolum (108)	Sulfamethoxazole
Thiamphenicolum (109)	Thiamphenicol

Texts of Part I

VI.1.2.1.1. Materials based on plasticised poly(vinyl chloride) for containers for human blood and blood components.

VI.2.2.1. Plastic containers and closures.

VI.2.2.2.1. Sterile plastic containers for human blood and blood components.

VI.2.2.2.2. Empty sterile containers of plasticised poly(vinyl chloride) for human blood and blood components.

VI.2.2.2.3. Sterile containers of plasticised poly(vinyl chloride) for human blood containing an anticoagulant solution.

ERRATA

Part I

IV. GENERAL NOTICES.

Abbreviations used in the monographs on immunosera and vaccines.

Lp/10 dose. line 3. For " does not cause ", read " causes ".

V.2.2.5. ASSAY OF BLOOD COAGULATION FACTOR VIII.

Seventh paragraph, last line. For " activation ", read " activator formation ".

V.3.5.2. DETERMINATION OF NITROGEN BY SULPHURIC ACID DIGESTION.

First paragraph, third line. For " potassium sulphate R ", read " dipotassium sulphate R ".

Part II

RIFAMPICINUM

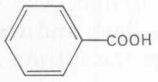
Add at the end of the monograph:

VII.1.3. BUFFER SOLUTIONS

Buffer (phosphate) solution pH 6.0 Mix 63.2 ml of a 7.15 per cent *m/V* solution of disodium hydrogen phosphate R and 36.8 ml of a 2.1 per cent *m/V* solution of citric acid R.

ACIDUM BENZOICUM

Benzoic Acid



$C_7H_6O_2$ M_r 122.1

Benzoic acid contains not less than 99.0 per cent and not more than the equivalent of 100.5 per cent of benzenecarboxylic acid.

CHARACTERS

A white, crystalline powder or colourless crystals, odourless or with a very slight characteristic odour, slightly soluble in water, soluble in boiling water, freely soluble in alcohol, in chloroform, in ether and in fatty oils.

IDENTIFICATION

A. Melting point (V.6.11.1): 121 °C to 124 °C.

B. Solution S (see Tests) gives reaction (a) of benzoates (V.3.1.1).

TESTS

Solution S Dissolve 5.0 g in alcohol R and dilute to 100 ml with the same solvent.

Appearance of solution Solution S is clear (V.6.1) and colourless (Method II, V.6.2).

Carbonisable substances Dissolve 0.5 g with shaking in 5 ml of sulphuric acid R. After 5 min, the solution is not more intensely coloured than reference solution Y_5 (Method I, V.6.2).

Oxidisable substances Dissolve 0.2 g in 10 ml of boiling water. Cool, shake and filter. To the filtrate add 1 ml of dilute sulphuric acid R and 0.2 ml of 0.1N potassium permanganate. After 5 min, the solution is still coloured pink.

Halogenated compounds and halides (1)

Solution (a) Dissolve 6.7 g of the substance to be examined in a mixture of 40 ml of 1N sodium hydroxide and 50 ml of alcohol R and dilute to 100.0 ml with water. To 10.0 ml of this solution add 7.5 ml of dilute sodium hydroxide solution R and 0.125 g of nickel-aluminium alloy R and heat on a water-bath for 10 min. Allow to cool to room temperature, filter into a 25 ml volumetric flask and wash with three quantities, each of 2 ml, of alcohol R. Dilute the filtrate and washings to 25.0 ml with water. This solution is used to prepare solution A.

Solution (b) In the same manner, prepare a similar solution without the substance to be examined. This solution is used to prepare solution B.

In four 25 ml volumetric flasks, place separately 10 ml of solution (a), 10 ml of solution (b), 10 ml of chloride standard solution (8 ppm Cl) R (used to prepare solution C) and 10 ml of water. To each flask add 5 ml of ferric ammonium sulphate solution R5, mix and add dropwise and with swirling 2 ml of nitric acid R and 5 ml of mercuric thiocyanate solution R. Shake. Dilute the contents of each flask to 25.0 ml with water and allow the solutions to stand in a water-bath at 20 °C for 15 min. Measure at 460 nm the absorbance (V.6.19) of solution A using solution B as the compensation liquid, and the absorbance of solution C using the solution obtained with 10 ml of water as the compensation liquid. The absorbance of solution A is not greater than that of solution C (300 ppm).

Heavy metals (V.3.2.8) 12 ml of solution S complies with limit test B for heavy metals (10 ppm). Prepare the standard using a mixture of 5 ml of lead standard solution (1 ppm Pb) and 5 ml of alcohol R.

Sulphated ash (V.3.2.14) Not more than 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.200 g in 20 ml of alcohol R and titrate with 0.1N sodium hydroxide, using 0.1 ml of phenol red solution R as indicator, until the colour changes from yellow to violet-red.

1 ml of 0.1N sodium hydroxide is equivalent to 12.21 mg of $C_7H_6O_2$.

VII.1.1. REAGENTS

Ferric ammonium sulphate

Ferric ammonium sulphate solution R5 Shake 30.0 g of ferric ammonium sulphate R with 40 ml of nitric acid R and dilute to 100 ml with water. If the solution is turbid, centrifuge or filter it. Store protected from light.

(1) All glassware used must be chloride-free and may be prepared by soaking overnight in a 50 per cent *m/V* solution of nitric acid R, rinsed with water and stored full of water. It is recommended that glassware be reserved for this test.

Mercuric thiocyanate. — $Hg(SCN)_2$ (M_r 316.8).

A white, crystalline powder, very slightly soluble in water, slightly soluble in alcohol and in ether, soluble in solutions of sodium chloride.

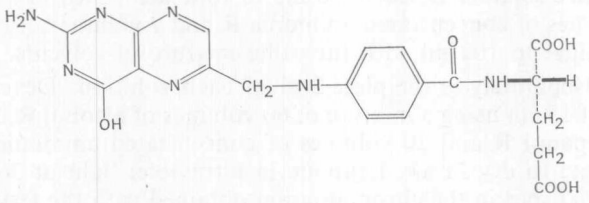
Mercuric thiocyanate solution Dissolve 0.3 g of mercuric thiocyanate R in ethanol R and dilute to 100 ml with the same solvent. The solution is stable for about one week.

VII.1.2. STANDARD SOLUTIONS FOR LIMIT TESTS

Chloride standard solution (8 ppm Cl) Immediately before use, dilute with water to 100 times its volume a solution containing sodium chloride R equivalent to 1.32 g of NaCl in 1000.0 ml.

ACIDUM FOLICUM

Folic Acid



$C_{19}H_{19}N_7O_6$ M_r 441.4

Folic acid contains not less than 96.0 per cent and not more than the equivalent of 102.0 per cent of (2*S*)-2-{4-[(2-amino-4-hydroxypteridin-6-yl)methylamino]benzamido}glutaric acid, calculated with reference to the dried substance.

CHARACTERS

A yellowish to orange, crystalline powder, odourless or almost odourless, practically insoluble in water and in most organic solvents. It dissolves in dilute acids and in alkaline solutions.

IDENTIFICATION

A. Dissolve 0.25 g in 0.1N sodium hydroxide and dilute to 25.0 ml with the same solvent. The specific optical rotation (V.6.6) is about +20°, calculated with reference to the dried substance.

B. Dissolve 10 mg in 0.1N sodium hydroxide and dilute to 100.0 ml with the same solvent. Dilute 5.0 ml of this solution to 50.0 ml with 0.1N sodium hydroxide. Examined between 230 nm and 380 nm (V.6.19), the solution shows three absorption maxima, at 256 nm, 283 nm and 365 nm. The specific absorbances at these maxima are about 590, 575 and 206, respectively, calculated with reference to the dried substance. The ratio of the specific absorbance at 256 nm to that at 365 nm is 2.8 to 3.0.

C. Examine by thin-layer chromatography (V.6.20.2), using silica gel G R as the coating substance.

Test solution Dissolve 50 mg of the substance to be examined in a mixture of 2 volumes of concentrated ammonia R and 9 volumes of methanol R and dilute to 100 ml with the same mixture of solvents.

Reference solution Dissolve 50 mg of folic acid CRS in a mixture of 2 volumes of concentrated ammonia R and 9 volumes of methanol R and dilute to 100 ml with the same mixture of solvents.

Apply separately to the plate 2 µl of each solution. Develop over a path of 15 cm using a mixture of 60 volumes of alcohol R, 20 volumes of propanol R and 20 volumes of concentrated ammonia R. Allow the plate to dry in air. Examine in ultraviolet light at 365 nm. The principal spot in the chromatogram obtained with the test solution is similar in position, fluorescence and size to the principal spot in the chromatogram obtained with the reference solution.

TESTS

Free amines The absorbance A_2 is not more than one-sixth of the absorbance A_1, as determined in the assay.

Loss on drying (V.6.22) 5.0 per cent to 8.5 per cent, determined on 1.00 g by drying at 100 °C to 105 °C at a pressure not exceeding 670 Pa (5 Torr) for 3 h.

Sulphated ash (V.3.2.14) Not more than 0.2 per cent, determined on 1.0 g.

ASSAY

Dissolve 50.0 mg in 50 ml of 0.1N sodium hydroxide and dilute to 100.0 ml with the same solvent (solution a).

(1) To 3.0 ml of solution (a) add 20 ml of dilute hydrochloric acid R and dilute to 100.0 ml with water. To 50.0 ml of this solution add 0.5 g of zinc powder R, allow to stand protected from light for 20 min with frequent shaking and filter. Discard the first 10 ml of the filtrate, then take 10.0 ml and dilute to 25.0 ml with water. Add 5 ml of dilute hydrochloric acid R and 5 ml of a 0.1 per cent m/V solution of sodium nitrite R, mix and allow to stand for 2 min. Add 5 ml of a 0.5 per cent m/V solution of ammonium sulphamate R, mix and allow to stand for 2 min. Add 5 ml of a 0.1 per cent m/V solution of naphthylethylenediamine dihydrochloride R, mix and allow to stand for 10 min. Dilute to 50.0 ml with water and measure the absorbance (A_1) of this reduced solution (V.6.19) at the maximum at 550 nm, using as the compensation liquid a mixture of 25.0 ml of water, 5 ml of dilute hydrochloric acid R and 5 ml of a 0.1 per cent m/V solution of sodium nitrite R, treated as described above.

(2) To 30.0 ml of solution (a) add 20 ml of dilute hydrochloric acid R and dilute to 100.0 ml with water. Dilute 10.0 ml of this solution to 25.0 ml with water, add 5 ml of dilute hydrochloric acid R, 5 ml of a 0.1 per cent m/V solution of sodium nitrite R, treat as described above, and measure the absorbance (A_2) of this non-reduced solution.

Repeat the operations described above using folic acid CRS, the absorbance of the reduced solution being A_3 and that of the non-reduced solution A_4.

Calculate the content of $C_{19}H_{19}N_7O_6$ in the substance to be examined using the expression:

$$\frac{A_1 - 0.1A_2}{A_3 - 0.1A_4} \times C$$

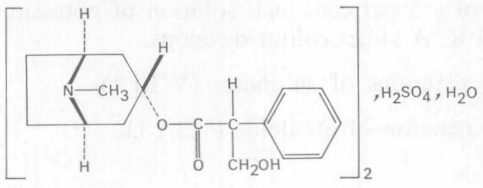
C = the declared content of $C_{19}H_{19}N_7O_6$ in folic acid CRS.

STORAGE

Store in a well-closed container, protected from light.

ATROPINI SULFAS

Atropine Sulphate



$C_{34}H_{48}N_2O_{10}S,H_2O$ M_r 695

Atropine sulphate contains not less than 99.0 per cent and not more than the equivalent of 101.0 per cent of bis {(1*R*,3*r*,5*S*)-3-[(*RS*)-(3-hydroxy-2-phenylpropionyl)oxy]-8-methyl-8-azabicyclo[3.2.1]octane} sulphate, calculated with reference to the anhydrous substance.

CHARACTERS

A white, crystalline powder or colourless crystals, odourless, very soluble in water, freely soluble in alcohol, practically insoluble in chloroform and in ether.

It melts at about 190 °C with decomposition, determined on the substance dried at 135 °C for 15 min.

IDENTIFICATION

Identification tests A and B may be omitted if identification tests C, D, E and F are carried out. Identification tests C, D and F may be omitted if identification tests A, B and E are carried out.

A. An aqueous solution shows almost no optical rotation (see Tests).

B. Examine by infrared absorption spectrophotometry (V.6.18). The absorption maxima in the spectrum obtained with the substance to be examined correspond in position and relative intensity to those in the spectrum obtained with atropine sulphate CRS.

C. Dissolve about 50 mg in 5 ml of water and add 5 ml of picric acid solution R. The precipitate, washed with water and dried at 100 °C to 105 °C for 2 h, melts (V.6.11.1) at 174 °C to 179 °C.

D. To about 1 mg add 0.2 ml of fuming nitric acid R and evaporate to dryness in a water-bath. Dissolve the residue in 2 ml of acetone R and add 0.1 ml of a 3 per cent *m/V* solution of potassium hydroxide R in methanol R. A violet colour develops.

E. It gives the reactions of sulphates (V.3.1.1).

F. It gives the reaction of alkaloids (V.3.1.1).

TESTS

pH (V.6.3.1) Dissolve 0.6 g in carbon dioxide-free water R and dilute to 30 ml with the same solvent. The pH of the solution is 4.5 to 6.2.

Optical rotation (V.6.6) Dissolve 2.50 g in water and dilute to 25.0 ml with the same solvent. The angle of optical rotation measured in a 2-dm tube is – 0.50° to + 0.05°.

Foreign alkaloids and decomposition products Examine by thin-layer chromatography (V.6.20.2), using silica gel G R as the coating substance.

Test solution Dissolve 0.2 g of the substance to be examined in methanol R and dilute to 10 ml with the same solvent.

Reference solution (a) Dilute 1 ml of the test solution to 100 ml with methanol R.

Reference solution (b) Dilute 5 ml of reference solution (a) to 10 ml with methanol R.

Apply separately to the plate 10 µl of each solution. Develop over a path of 10 cm using a mixture of 90 volumes of acetone R, 7 volumes of water and 3 volumes of concentrated ammonia R. Dry the plate at 100 °C to 105 °C for 15 min. Allow to cool and spray with dilute potassium iodobismuthate solution R until the spots appear. 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 reference solution (a) and not more than one such spot is more intense than the spot in the chromatogram obtained with reference solution (b).

Apoatropine Dissolve 0.10 g in 0.01N hydrochloric acid and dilute to 100.0 ml with the same acid. Determine the absorbance (V.6.19) at 245 nm. The specific absorbance is not greater than 4.0, calculated with reference to the anhydrous substance (about 0.5 per cent).

Water (V.3.5.6) 2.0 per cent to 4.0 per cent, determined on 0.50 g by the semi-micro determination of water.

Sulphated ash (V.3.2.14) Not more than 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.500 g in 30 ml of anhydrous acetic acid R, warming if necessary. Cool the solution. Carry out the non-aqueous titration of organic bases (V.3.5.5), titrating with 0.1N perchloric acid and determining the end-point potentiometrically (V.6.14).

1 ml of 0.1N perchloric acid is equivalent to 67.68 mg of $C_{34}H_{48}N_2O_{10}S$.

STORAGE

Store in a well-closed container, protected from light.