The International Pharmacopoeia

Fourth edition

Volume 2

World Health Organization

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SELECTED WHO PUBLICATIONS OF RELATED INTEREST

Basic tests for drugs:
pharmaceutical substances, medicinal plant materials and dosage forms
1998 (94 pages)

Basic tests for pharmaceutical dosage forms
1991 (134 pages)

Quality Assurance of Pharmaceuticals: a compendium of guidelines and related materials
Volume 1: 1997 (244 pages)
Volume 2: good manufacturing practices and inspection. 2004 (236 pages)

WHO Expert Committee on Specifications for Pharmaceutical Preparations
Fortieth report
WHO Technical Report Series, No. 937,
2006 (461 pages)

International nonproprietary names (INN) for pharmaceutical substances
Cumulative list no. 11
2004 (available in CD-ROM format only)

The use of essential medicines
Report of the WHO Expert Committee
(including the 13th Model List of Essential Medicines)
WHO Technical Report Series, No. 920,
2004 (133 pages)

WHO Expert Committee on Biological Standardization
Fifty-fourth report
WHO Technical Report Series, No. 927,
2005 (160 pages)

Further information on these or other WHO publications can be obtained from WHO Press, World Health Organization, 1211 Geneva 27, Switzerland.
Attention is also drawn to the WHO Medicines web site
(http://www.who.int/medicines)

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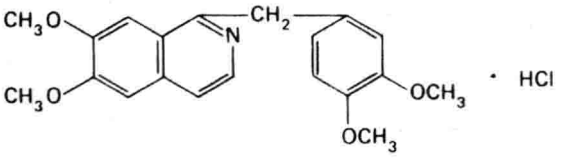
PAPAVERINI HYDROCHLORIDUM
PAPAVERINE HYDROCHLORIDE

Molecular formula. $C_{20}H_{21}NO_4,HCl$

Relative molecular mass. 375.9

Graphic formula.



Chemical name. 6,7-Dimethoxy-1-veratrylisoquinoline hydrochloride; 1-[(3,4-dimethoxyphenyl)methyl]-6,7-dimethoxyisoquinoline hydrochloride; CAS Reg. No. 61-25-6.

Description. Colourless crystals or a white, crystalline powder; odourless.

Solubility. Sparingly soluble in water; soluble in 120 parts of ethanol (~750 g/l) TS; practically insoluble in ether R.

Category. Spasmolytic.

Storage. Papaverine hydrochloride should be kept in a well-closed container, protected from light.

Requirements

Definition. Papaverine hydrochloride contains not less than 98.5% and not more than 101.0% of $C_{20}H_{21}NO_4,HCl$, calculated with reference to the dried substance.

Identity tests

- Either tests A and C or tests B, C, and D may be applied.

A. Carry out the examination as described under 1.7 Spectrophotometry in the infrared region. The infrared absorption spectrum is concordant with the spectrum obtained from papaverine hydrochloride RS or with the *reference spectrum* of papaverine hydrochloride.

B. Treat about 10 mg with 3 ml of acetic anhydride R, add cautiously 3 drops of sulfuric acid (~1760 g/l) TS and heat on a water-bath for 3–4 minutes; a yellow colour with a green fluorescence is produced.

C. A 20 mg/ml solution yields reaction B described under 2.1 General identification tests as characteristic of chlorides.

D. Dissolve 20 mg in 10 ml of water, add drop by drop ammonia (~100 g/l) TS, and set aside. Filter, wash the precipitate with water, and dry at 105 °C; melting temperature, about 146 °C (papaverine base).

Clarity and colour of solution. A solution of 0.20 g in 10 ml of carbon-dioxide-free water R is clear and not more intensely coloured than standard colour solution Gn2 when compared as described under 1.11 Colour of liquids.

Sulfated ash. Not more than 1.0 mg/g.

Loss on drying. Dry to constant weight at 105 °C; it loses not more than 10 mg/g.

pH value. pH of a 20 mg/ml solution, 3.0–4.5.

Related substances. Carry out the test as described under 1.14.1 Thin-layer chromatography, using silica gel R2 as the coating substance and a mixture of 7 volumes of toluene R, 2 volumes of ethyl acetate R, and 1 volume of diethylamine R as the mobile phase. Apply separately to the plate 10 µl of each of 2 solutions in a mixture of 4 volumes of hydrochloric acid (0.01 mol/l) VS and 1 volume of ethanol (~750 g/l) TS containing (A) 0.050 g of the test substance per ml and (B) 0.50 mg of codeine R per ml. After removing the plate from the chromatographic chamber, allow it to dry in a current of warm air until the odour of diethylamine is no longer perceptible, and examine the chromatogram in ultraviolet light (254 nm). Any spot obtained with solution A, other than the principal spot, is not more intense than that obtained with solution B.

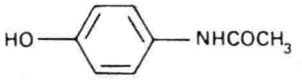
Assay. Dissolve about 0.35 g, accurately weighed, in 30 ml of glacial acetic acid R1, add 10 ml of mercuric acetate/acetic acid TS and titrate with perchloric acid (0.1 mol/l) VS as described under 2.6 Non-aqueous titration. Method A. Each ml of perchloric acid (0.1 mol/l) VS is equivalent to 37.59 mg of $C_{20}H_{21}NO_4,HCl$.

PARACETAMOLUM
PARACETAMOL

Molecular formula. $C_8H_9NO_2$

Relative molecular mass. 151.2

Graphic formula.



Chemical name. 4′-Hydroxyacetanilide; *N*-(4-hydroxyphenyl)acetamide; CAS Reg. No. 103-90-2.

Other name. Acetaminophen.

Description. A white, crystalline powder; odourless.

Solubility. Sparingly soluble in water; freely soluble in ethanol (~750 g/l) TS and acetone R; practically insoluble in ether R.

Category. Analgesic; antipyretic.

Storage. Paracetamol should be kept in a tightly closed container, protected from light.

Requirements

Definition. Paracetamol contains not less than 98.5% and not more than 101.0% of $C_8H_9NO_2$, calculated with reference to the dried substance.

Identity tests

A. Dissolve 0.05 g in 100 ml of methanol R. To 1 ml of this solution add 0.5 ml of hydrochloric acid (0.1 mol/l) VS and dilute to 100 ml with methanol R. Protect the solution from light and immediately measure the absorbance of a 1-cm layer at the maximum wavelength of about 249 nm; about 0.88.

B. Dissolve 0.1 g in 10 ml of water and add 0.05 ml of ferric chloride (25 g/l) TS; a violet-blue colour is produced.

C. Boil 0.1 g with 1 ml of hydrochloric acid (~70 g/l) TS for 3 minutes, add 10 ml of water and cool; no precipitate is formed. Add 0.05 ml of potassium

dichromate (0.0167 mol/l) VS; a violet colour, which does not turn to red (distinction from phenacetin) is slowly produced.

Melting range. 168–172 °C.

Heavy metals. Use 1.0 g and a mixture of 85 volumes of acetone R and 15 volumes of water for the preparation of the test solution as described under 2.2.3 Limit test for heavy metals, Procedure 2; determine the heavy metals content according to Method A; not more than 10 µg/g.

Sulfated ash. Not more than 1.0 mg/g.

Loss on drying. Dry to constant weight at 105 °C; it loses not more than 5.0 mg/g.

4-Aminophenol. Dissolve 0.5 g in a mixture of equal volumes of methanol R and water and dilute to 10 ml with this solvent mixture. Add 0.2 ml of alkaline sodium nitroprusside TS, mix, and allow to stand for 30 minutes. Prepare similarly a reference solution containing 0.5 g of 4-aminophenol-free paracetamol R and 0.5 ml of a solution containing 0.050 mg/ml of 4-aminophenol R in the same solvent mixture. The colour of the test solution is not more intense than that of the reference solution (0.05 mg/g).

Related substances. Carry out the test as described under 1.14.1 Thin-layer chromatography, using silica gel R4 as the coating substance and a mixture of 65 volumes of chloroform R, 25 volumes of acetone R, and 10 volumes of toluene R as the mobile phase. Allow the solvent front to ascend 14 cm above the line of application, using an unlined chromatographic chamber. Prepare the following 4 test solutions: For solution (A) transfer 1.0 g of finely powdered substance to be examined to a glass-stoppered tube, add 5 ml of ether R, and shake mechanically for 30 minutes. Centrifuge the tube until a clear supernatant liquid is obtained and separate this from the solid. For solution (B) dilute 1 ml of solution A to 10 ml with ethanol (~750 g/l) TS. For solution (C) dissolve 25 mg of 4-chloroacetanilide R in 50 ml of ethanol (~750 g/l) TS. For solution (D) dissolve 0.25 g of 4-chloroacetanilide R and 0.1 g of the substance to be examined in sufficient ethanol (~750 g/l) TS to produce 100 ml. Apply separately to the plate 200 µl of solution A and 40 µl of each of the remaining 3 solutions. After removing the plate from the chromatographic chamber, allow it to dry in a current of warm air and examine the chromatogram in ultraviolet light (254 nm). Any spot due to 4-chloroacetanilide obtained with solution A is not more intense than the corresponding spot obtained with solution C. Any spot obtained with solution B, other than the principal spot and the spot corresponding to 4-chloroacetanilide, is not more intense than the spot obtained with solution C. The test is valid only if the chromatogram obtained with solution D shows two distinctly separated spots corresponding to 4-chloroacetanilide and the substance being examined, the latter having a lower R_f value.

Assay. Transfer about 0.25 g, accurately weighed, to a flask, add 10 ml of hydrochloric acid (~70 g/l) TS and boil under a reflux condenser for 1 hour. Wash the condenser with 30 ml of water, add 1 g of potassium bromide R to the combined solution, and proceed as described under 2.7 Nitrite titration, titrating with sodium nitrite (0.1 mol/l) VS. Each ml of sodium nitrite (0.1 mol/l) VS is equivalent to 15.12 mg of $C_8H_9NO_2$.

PARAFFINUM ALBUM
WHITE, SOFT PARAFFIN

PARAFFINUM FLAVUM
YELLOW SOFT PARAFFIN

Chemical name. White and yellow petrolatum.

Other names. White petrolatum, yellow petrolatum; vaselinum album, vaselinum flavum.

Description. A white or a pale yellow to yellow, soft, unctuous mass; odourless.

Solubility. Practically insoluble in water and ethanol (~750 g/l) TS; soluble in ether R, and in most fixed and volatile oils.

Category. Ointment base.

Storage. White and yellow soft paraffins should be kept in a well-closed container.

Additional information. In a thin layer or when melted, both paraffins show a slight fluorescence. Melting point, within 38–60 °C.

Requirements

Definition. White and yellow soft paraffins are purified mixtures of semi-solid hydrocarbons obtained from petroleum. White soft paraffin is bleached. To prevent oil separation, soft paraffins may contain a suitable stabilizer.

Identity tests

A. Melt 2 g until a homogeneous mass is obtained and immediately add 2 ml of water and 0.2 ml of iodine (0.1 mol/l) VS. Heat; as soon as two liquid phases are obtained, shake and cool; the upper solid phase should have a pinkish violet colour.

B. Heat a small quantity of either White soft paraffin or Yellow soft paraffin and ignite; a luminous flame is observed and a deposit of carbon is formed.

Sulfated ash. Not more than 1.0 mg/g.

Alkalinity. To 35 g add 100 ml of boiling water, cover the beaker, and, while stirring, heat to boiling for 5 minutes. Allow the phases to separate, transfer the aqueous layer to a suitable dish, and wash the paraffin with two portions, each of 50 ml, of boiling water which are added to the dish. Add 1 drop of phenolphthalein/ethanol TS and boil; the colour does not change to pink. (Keep this solution for "Acidity".)

Acidity. To the above solution, add 0.1 ml of methyl orange/ethanol TS; the colour does not change to red or pink.

Organic acids. To 20 g add 100 ml of a mixture of equal volumes of neutralized ethanol TS and water, mix thoroughly, and heat to boiling. Add 1 ml of phenolphthalein/ethanol TS and titrate rapidly with carbonate-free sodium hydroxide (0.1 mol/l) VS to a sharp pink endpoint, the colour change being observed in the ethanol-water layer; not more than 0.4 ml of carbonate-free sodium hydroxide (0.1 mol/l) VS is required.

Fixed oils, fats, and rosin. Digest 10 g with 50 ml of sodium hydroxide (~200 g/l) TS at 100 °C for 30 minutes. Separate the aqueous layer and acidify with sulfuric acid (~570 g/l) TS; the remaining phase does not show any oil or solid matter.

Ultraviolet absorption. Dissolve 50 mg in 100 ml of 2,2,4-trimethylpentane R. Measure the absorbance of a 1-cm layer at about 290 nm. White soft paraffin does not exceed 0.5; yellow soft paraffin does not exceed 0.75.

PARAFFINUM DURUM
HARD PARAFFIN

Chemical name. Paraffin wax; paraffin waxes and hydrocarbon waxes; CAS Reg. No. 8002-74-2.

Description. A colourless or white, slightly unctuous mass showing a crystalline structure; odourless.

Solubility. Practically insoluble in water and ethanol (~750 g/l) TS; freely soluble in ether R.

Category. Ointment base; viscosity-increasing agent.

Storage. Hard paraffin should be kept in a well-closed container.

Additional information. Congealing point, within 47–65 °C.

Requirements

Definition. Hard paraffin is a purified mixture of solid hydrocarbons obtained from petroleum.

Identity tests

A. Melt 2 g until a homogeneous mass is obtained and immediately add 2 ml of water and 0.2 ml of iodine (0.1 mol/l) VS. Heat; as soon as two liquid phases are obtained, shake and cool; the upper solid phase has a pinkish violet colour.

B. Heat a small quantity of Hard paraffin and ignite; a luminous flame is observed and a deposit of carbon is formed.

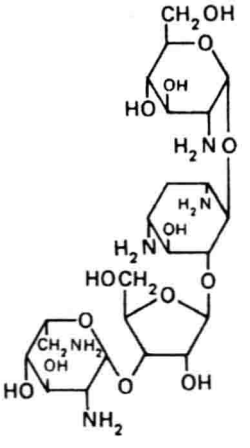
Sulfated ash. Not more than 1.0 mg/g.

Acidity or alkalinity. Boil 5 g with 10 ml of ethanol (~710 g/l) TS previously neutralized to litmus TS, cool, and add a few drops of litmus TS; the solution is neutral (violet).

PAROMOMYCINI SULFAS
PAROMOMYCIN SULFATE

Molecular formula. $C_{23}H_{45}N_5O_{14},xH_2SO_4$

Graphic formula.



Chemical name. *O*-2,6-Diamino-2,6-dideoxy-β-L-idopyranosyl-(1→3)-*O*-β-D-ribofuranosyl-(1→5)-*O*-[2-amino-2-deoxy-α-D-glucopyranosyl-(1→4)]-2-deoxystreptamine sulfate (salt); *O*-2-amino-2-deoxy-α-D-glucopyranosyl-(1→4)-*O*-[*O*-2,6-diamino-2,6-dideoxy-β-L-idopyranosyl-(1→3)-β-D-ribofuranosyl-(1→5)]-2-deoxy-D-streptamine sulfate (salt); CAS Reg. No. 1263-89-4.

Description. A creamy white to light yellow powder; odourless or almost odourless.

Solubility. Very soluble in water; practically insoluble in ethanol (~750 g/l) TS and ether R.

Category. Antiamoebic drug.

Storage. Paromomycin sulfate should be kept in a tightly closed container, protected from light.

Additional information. Paromomycin sulfate is very hygroscopic. Even in the absence of light, it is gradually degraded on exposure to a humid atmosphere, the decomposition being faster at higher temperatures.

Requirements

Definition. Paromomycin sulfate contains not less than 675 International Units of paromomycin per mg, calculated with reference to the dried substance.

Identity tests

A. Carry out the test as described under 1.14.1 Thin-layer chromatography, using silica gel R3 as the coating substance and a freshly prepared ammonium acetate (40 g/l) TS as the mobile phase. Apply separately to the plate 1 µl of each of 2 solutions containing (A) 20 mg of the test substance per ml and (B) 20 mg of paromomycin sulfate RS per ml. After removing the plate from the chromatographic chamber, allow it to dry in air for 10 minutes, heat it at 105 °C for 1 hour, and spray it with triketohydrindene/butanol TS. Heat it again at 105 °C for 5 minutes and examine the chromatogram in daylight. The principal red spot obtained with solution A corresponds in position and appearance with that obtained with solution B.

B. A 0.05 g/ml solution yields reaction A described under 2.1 General identification tests as characteristic of sulfates.

Specific optical rotation. Use a 50 mg/ml solution and calculate with reference to the dried substance; $[\alpha]_D^{20\,°C}$ = +50 to +55 °.

Sulfated ash. Not more than 20 mg/g.

Loss on drying. Dry to constant weight at 50 °C under reduced pressure (not exceeding 0.6 kPa or about 5 mm of mercury); it loses not more than 50 mg/g.

pH value. pH of a 30 mg/ml solution in carbon-dioxide-free water R, 5.0–7.5.

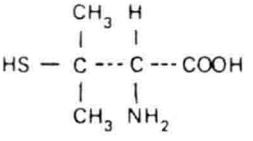
Assay. Carry out the assay as described under 3.1 Microbiological assay of antibiotics, using either (*a*) *Bacillus subtilis* (NCTC 10400) as the test organism, culture medium Cm1 with a final pH of 8.0, sterile phosphate buffer pH 7.8, TS, an appropriate concentration of paromomycin (usually between 1 and 4 IU per ml), and an incubation temperature of 37–39 °C; or (*b*) *Bacillus subtilis* (ATCC 6633) as the test organism, culture medium Cm1 with a final pH of 7.8, sterile phosphate buffer pH 8.0, TS1 or TS2, an appropriate concentration of paromomycin (usually between 2 and 8 IU per ml), and an incubation temperature of 36–38 °C. The precision of the assay is such that the fiducial limits of error of the estimated potency ($P = 0.95$) are not less than 95% and not more than 105% of the estimated potency. The upper fiducial limit of error of the estimated potency ($P = 0.95$) is not less than 675 IU of paromomycin per mg, calculated with reference to the dried substance.

PENICILLAMINUM
PENICILLAMINE

Molecular formula. $C_5H_{11}NO_2S$

Relative molecular mass. 149.2

Graphic formula.



Chemical name. 3-Mercapto-D-valine; 3,3-dimethyl-D-cysteine; CAS Reg. No. 52-67-5.

Description. A white or almost white, crystalline powder; odour, characteristic.

Solubility. Soluble in 9 parts of water; slightly soluble in ethanol (~750 g/l) TS; practically insoluble in chloroform R and ether R.

Category. Antidote.

Storage. Penicillamine should be kept in a tightly closed container, protected from light.

Additional information. Even in the absence of light, Penicillamine is gradually degraded on exposure to a humid atmosphere, the decomposition being faster at higher temperatures.

Requirements

Definition. Penicillamine contains not less than 95.0% and not more than 100.5% of $C_5H_{11}NO_2S$, calculated with reference to the dried substance.

Identity tests

A. Dissolve 20 mg in 4 ml of water, add 2 ml of phosphotungstic acid TS and allow to stand for a few minutes; a deep blue colour is produced.

B. Dissolve 20 mg in 5 ml of water, add 0.05 ml of sodium hydroxide (~200 g/l) TS and 20 mg of triketohydrindene hydrate R; an intense blue or violet-blue colour is produced immediately.

Specific optical rotation. Use a 50 mg/ml solution in sodium hydroxide (1 mol/l) VS; $[\alpha]_D^{20\,°C} = -58$ to $-68\,°$.

Sulfated ash. Not more than 1.0 mg/g.

Loss on drying. Dry to constant weight at 60 °C under reduced pressure (not exceeding 0.6 kPa or about 5 mm of mercury); it loses not more than 5 mg/g.

pH value. pH of a 10 mg/ml solution, 4.0–6.0.

Mercury

- The operations described below must be carried out in subdued light.

Transfer about 0.5 g, accurately weighed, to a 650-ml long-necked flask containing a few glass beads, incline the flask at an angle of about 45 °, and add 2.5 ml of nitric acid (~1000 g/l) TS through a small funnel placed in the mouth of the flask. Allow the mixture to stand at room temperature until nitrous oxide fumes are evolved and the vigorous reaction subsides (5–30 minutes). Add 2.5 ml of sulfuric acid (~1760 g/l) TS through the funnel and heat, gently at first and then to the production of fumes of sulfur trioxide. Cool, then add cautiously 2.5 ml of nitric acid (~1000 g/l) TS, heat again to the production of sulfur trioxide fumes, and cool. Repeat this treatment once more, then add 50 ml of water, rinsing the funnel, and collecting the rinsings in the flask. Remove the funnel, boil the solution down to approximately half its volume (about 25 ml), and cool to room temperature. Transfer to a 250-ml separating funnel with the

aid of water and dilute with water to 50 ml. Add 1 ml of disodium edetate (20 g/l) TS and 1 ml of glacial acetic acid R and extract with small portions of chloroform R until the last chloroform extract remains colourless. Discard the chloroform extract and add 50 ml of sulfuric acid (0.125 mol/l) VS, 90 ml of water, and 10 ml of hydroxylamine hydrochloride (200 g/l) TS. Add dithizone standard TS, in portions of 0.3–0.5 ml, from a 10-ml burette. After each addition, shake the mixture well, allow the chloroform layer to separate, and discard it. Continue until an addition of dithizone standard TS remains green after shaking.

From the volume of the dithizone standard TS used, calculate the amount of mercury present in the test substance. It contains not more than 20 µg of Hg per g.

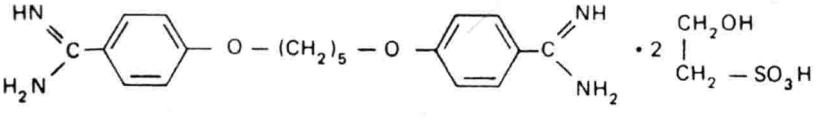
Assay. Dissolve about 0.1 g, accurately weighed, in 50 ml of water, add 5 ml of sodium hydroxide (1 mol/l) VS and 0.2 ml of dithizone TS and titrate with mercuric nitrate (0.02 mol/l) VS. Each ml of mercuric nitrate (0.02 mol/l) VS is equivalent to 5.968 mg of $C_5H_{11}NO_2S$.

PENTAMIDINI ISETIONAS
PENTAMIDINE ISETIONATE

Molecular formula. $C_{19}H_{24}N_4O_2,2C_2H_6O_4S$

Relative molecular mass. 592.7

Graphic formula.



Chemical name. 4,4′-(Pentamethylenedioxy)dibenzamidine bis(2-hydroxyethanesulfonate); 4,4′-[1,5-pentanediylbis(oxy)]bis[benzenecarboximidamide]-bis(2-hydroxyethanesulfonate); CAS Reg. No. 140-64-7.

Description. A white, or almost white, crystalline powder; odourless.

Solubility. Soluble in 10 parts of water; slightly soluble in ethanol (~750 g/l) TS; practically insoluble in chloroform R and ether R.

Category. Antitrypanosomal drug; antileishmaniasis drug.