



THE INTERNATIONAL PHARMACOPOEIA
THIRD EDITION

PHARMACOPOEIA INTERNATIONALIS
EDITIO TERTIA

VOLUME 5

DRAFT MONOGRAPHS FOR
TABLETS

Comments are invited to review individual monographs for tablets to be included in volume 5 of *The International Pharmacopoeia, third edition*. Kindly address your proposals to Dr A. Mechkovski, Drug Management and Policies, Quality Assurance, World Health Organization, 1211 Geneva 27, Switzerland, within two months of the date of mailing.

Contents

| | page |
|-----------------|------|
| 1. Introduction | 1 |
| 2. Monographs | 2 |
| 3. Reagents | 37 |

1. Introduction

The selection of monographs for *The International Pharmacopoeia* is determined by the WHO Model List of Essential Drugs, which is periodically updated. Monographs for the majority of substances are included in volumes 2, 3 and 4 of *The International Pharmacopoeia*. Volume 4 contains 22 monographs for tablets and the 20 draft monographs described in this document have not been included in previous volumes.

When formulating your comments, we would be grateful if you would refer to the "Guidance for those preparing or commenting on monographs for preparations to be included in *The International Pharmacopoeia*".

The draft text "Dissolution test for solid oral dosage forms" (WHO/PHARM/94.570) is in preparation and is expected to be finalized by the end of 1994. Specifications for individual monographs are under discussion and will be added at a later date to monographs already published in volume 4 and to the following monographs: Carbamazepine tablets, Doxycycline hyclate tablets, Erythromycin ethylsuccinate tablets, Erythromycin stearate tablets, Ethambutol hydrochloride, Ibuprofen tablets, Indometacin tablets, Isoniazid tablets and Phenytoin sodium tablets.

* WHO Technical Report Series, No. 790, 1990 (Thirty-first report of the WHO Expert Committee on Specifications for Pharmaceutical Preparations), Annex 3.

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Les opinions exprimées dans les documents par des auteurs cités nommément n'engagent que lesdits auteurs.

It would be desirable to add a test for related substances to all monographs for tablets. The following monographs would still need a proposal: Codeine phosphate tablets, Dexamethasone tablets, Doxycycline hyclate tablets, Erythromycin ethylsuccinate tablets, Erythromycin stearate tablets, Morphine sulfate tablets and Phenobarbital tablets.

In the monograph for Dexamethasone tablets, it would be desirable to change the method for the "Uniformity of Content" from an HPLC-technique to a UV-method, if feasible. Suggestions are invited.

2. Monographs

| | <i>Page</i> |
|---|-------------|
| Allopurinoli compressi | 2 |
| Carbamazepini compressi | 4 |
| Codeini phosphatis compressi | 5 |
| Colchicini compressi | 7 |
| Dexamethasoni compressi | 9 |
| Diloxanidi furoatis compressi | 11 |
| Doxycyclini hyclatis compressi | 12 |
| Erythromycini ethylsuccinatis compressi | 15 |
| Erythromycini stearatis compressi | 17 |
| Ethambutoli hydrochloridi compressi | 19 |
| Ibuprofeni compressi | 20 |
| Indometacini compressi | 22 |
| Isoniazidi compressi | 24 |
| Morphini sulfatis compressi | 25 |
| Pethidini hydrochloridi compressi | 26 |
| Phenobarbitali compressi | 28 |
| Phenytoini natrici compressi | 29 |
| Praziquanteli compressi | 31 |
| Prednisoloni compressi | 33 |
| Pyranteli embonatis compressi | 35 |

ALLOPURINOLI COMPRESSI

Allopurinol tablets

Category. Drug used for the treatment of gout.

Additional information. Strength in the current WHO Model list of essential drugs: 100 mg.

REQUIREMENTS

Complies with the monograph for "Tablets" (vol. 4, p. 26).

Allopurinol tablets contain not less than 90.0% and not more than 110.0% of the amount of $C_5H_4N_4O$ stated on the label.

Identity tests

- *Either test A alone or tests B and C may be applied.*

- A. Triturate a quantity of the powdered tablets equivalent to about 0.1 g of Allopurinol with 10 ml of sodium hydroxide (0.1 mol/l) VS. Filter, acidify the filtrate with acetic acid (~60 g/l) TS, and allow to stand for 10-15 minutes. Separate the precipitate, wash it with 3 ml of dehydrated ethanol R, and 4 ml of ether R. Allow to dry in air for 15 minutes, then dry at 105 °C for 3 hours. Keep half of the residue for test C. Carry out the examination with the residue as described under "Spectrophotometry in the infrared region" (vol. 1, p. 40). The infrared absorption spectrum is concordant with the spectrum obtained from allopurinol RS or with the *reference spectrum* of allopurinol.

- B. The absorption spectrum of the solution obtained in the "Assay", when observed between 230 nm and 350 nm, exhibits a maximum at about 250 nm.

- C. To the residue obtained in test A add 5 ml of sodium hydroxide (50 g/l) TS, 1.0 ml of alkaline potassium-mercuric iodide TS, heat to boiling and allow to stand; a yellow precipitate is produced.

Related substances. Carry out the test as described under "Thin-layer chromatography (vol. 1, p. 83), using silica gel R4 as the coating substance and a mixture of 6 volumes of 2-butanol R, 2 volumes of ammonia (~260 g/l) TS and 2 volumes of ethylene glycol monomethyl ether R as the mobile phase. Apply separately to the plate 10 µl of each of the following 2 solutions. For solution (A) shake a quantity of the powdered tablets equivalent to about 0.25 g of Allopurinol with a mixture of 1.0 ml of diethylamine R and 9 ml of water, filter and use the filtrate. For solution (B) use 0.05 mg of aminopyrazole-4-carboxamide hemisulfate RS per ml of ammonia (~260 g/l) TS. After removing the plate from the chromatographic chamber, allow it to dry in a current of air 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. Weigh and powder 20 tablets. To a quantity of the powder equivalent to about 0.1 g of Allopurinol add 20 ml of sodium hydroxide (0.05 mol/l) VS and shake for 20 minutes. Then add 80 ml of hydrochloric acid (0.1 mol/l) VS and shake for 10 minutes. Dilute to 250 ml with hydrochloric acid (0.1 mol/l) VS, filter, and

dilute 10 ml of the filtrate to 250 ml with the same acid. Measure the absorbance of a 1-cm layer at the maximum at about 250 nm, against a solvent cell containing hydrochloric acid (0.1 mol/l) VS.

Calculate the content of $C_5H_4N_4O$ using the absorptivity value of 56.3 ($A\ 1\%/1\ cm = 563$).

CARBAMAZEPINI COMPRESSI

Carbamazepine tablets

Category. Antiepileptic agent.

Storage. Carbamazepine tablets should be kept in a tightly closed container.

Additional information. Strength in the current WHO Model list of essential drugs: 100 mg, 200 mg.

REQUIREMENTS

Complies with the monograph for "Tablets" (vol. 4, p. 26).

Carbamazepine tablets contain not less than **90.0%** and not more than **110.0%** of the amount of $C_{15}H_{12}N_2O$ stated on the label.

Identity tests

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

Transfer a quantity of the powdered tablets equivalent to about 0.5 g of Carbamazepine to a 50-ml beaker, add 10 ml of warm acetone R and shake. Filter while still warm, evaporate the filtrate to dryness on a water-bath and dry at 80 °C. Dissolve in acetone R, allow to recrystallize and use the crystals for the following tests.

A. Carry out the examination with the crystals as described under "Spectrophotometry in the infrared region" (vol. 1, p. 40). The infrared absorption spectrum is concordant with the spectrum obtained from carbamazepine RS or with the *reference spectrum* of carbamazepine.

B. See the test described below under "Related substances". The principal spot obtained with solution A corresponds in position, appearance, and intensity with that obtained with solution B.

C. To about 0.1 g of the crystals add about 2 ml of nitric acid (~1000 g/l) TS and heat in a water-bath for 1 minute; an orange colour is produced.

D. Melting temperature of the residue, about 189 °C.

Related substances. Carry out the test as described under "Thin-layer chromatography (vol. 1, p. 83), using silica gel R1 as the coating substance and a mixture of 95 volumes of toluene R and 5 volumes of methanol R as the mobile phase. Apply separately to the plate 10 µl of each of the following 3 solutions. For solution (A) shake a quantity of the powdered tablets equivalent to about 0.20 g of Carbamazepine with three 10-ml quantities of chloroform R and filter. Evaporate the combined filtrates to dryness and dissolve the residue in 10 ml of chloroform R. For solution (B) use 20 mg of carbamazepine RS per ml of chloroform R. For solution (C) use 0.06 mg of iminodibenzyl R per ml of methanol R. After removing the plate from the chromatographic chamber, allow it to dry in air for 15 minutes, spray it with potassium dichromate TS3, and examine the chromatogram in daylight.

Any spot obtained with solution A, other than the principal spot, is not more intense than that obtained with solution C.

Assay. Weigh and powder 20 tablets. To a quantity of the powder equivalent to about 0.06 g of Carbamazepine add 25 ml of ethanol (~750 g/l) TS and boil for a few minutes. Stir the hot mixture in a closed flask for 10 minutes and filter through a sintered glass filter. Wash the flask and filter with ethanol (~750 g/l) TS, and dilute the cooled filtrate with sufficient ethanol (~750 g/l) TS to produce 100 ml. Dilute 5 ml to 250 ml with the same solvent. Measure the absorbance of a 1-cm layer at the maximum at about 285 nm, against a solvent cell containing ethanol (~750 g/l) TS.

Calculate the content of $C_{15}H_{12}N_2O$ using the absorptivity value of 49.0 ($A_{1\%}^{1\text{cm}} = 490$).

Dissolution. (See introduction).

CODEINI PHOSPHATIS COMPRESSI

Codeine phosphate tablets

Category. Opioid analgesic, antidiarrhoeal, antitussive.

Additional information. Strength in the current WHO Model list of essential drugs: 10 mg, 30 mg.

Codeine phosphate tablets are prepared either from the hemihydrate or the sesquihydrate.

REQUIREMENTS

Complies with the monograph for "Tablets" (vol. 4, p. 26).

Codeine phosphate tablets contain not less than 90.0% and not more than 110.0% of the amount of $C_{18}H_{21}NO_3 \cdot H_3PO_4$ stated on the label.

Identity tests

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

A. To a quantity of the powdered tablets equivalent to about 0.1 g of Codeine phosphate add 15 ml of water and 5 ml of sulfuric acid (~100 g/l) TS, and allow to stand for 1 hour. Filter, if necessary, and wash any undissolved residue with a few ml of water. Render the filtrate alkaline with ammonia (~100 g/l) TS and extract with several small portions of chloroform R. Evaporate the combined extracts to dryness on a water-bath, and dry the residue at 80 °C for 4 hours. Carry out the examination with the residue as described under "Spectrophotometry in the infrared region" (vol. 1, p. 40). The infrared absorption spectrum is concordant with the spectrum obtained from codeine phosphate RS or with the *reference spectrum* of codeine phosphate.

Shake a quantity of the powdered tablets equivalent to about 0.06 g of codeine phosphate with four 10-ml portions of ethanol (~750 g/l) TS and filter. Evaporate the combined filtrate to dryness on a water-bath and use the residue for the following tests.

B. Dissolve 10 mg of the residue in 5 ml of sulfuric acid (~1760 g/l) TS, add 1 drop of ferric chloride (25 g/l) TS and, if necessary, heat gently; a violet-blue colour is produced. Add a few drops of nitric acid (~130 g/l) TS; the colour changes to dark red.

C. Dissolve 20 mg of the residue in 1.0 ml of water and add 1 drop of ferric chloride (25 g/l) TS; a precipitate is formed but no blue tinge is observed in the solution (distinction from morphine).

D. Dissolve 10 mg of the residue in 2.0 ml of carbon-dioxide-free water R and add a few drops of silver nitrate (40 g/l) TS; a yellow precipitate is produced. Divide the solution with the precipitate into 2 portions. To 1 portion add a few drops of nitric acid (~130 g/l) TS; the precipitate dissolves to a clear solution. To the other portion add a few drops of ammonia (~100 g/l) TS and shake well; again the precipitate dissolves to a clear solution.

Assay. Weigh and powder 25 tablets. To a quantity of the powder equivalent to about 0.2 g of Codeine phosphate add sufficient water to produce a thin suspension, then add 20 ml of a mixture of 1 part of sulfuric acid (~100 g/l) TS and 3 parts of water. Shake occasionally during 2 hours, allow to stand for 12 hours and filter.

Add 5 ml of sodium hydroxide (~80 g/l) TS and extract with successive quantities of 15 ml, 10 ml, 10 ml and 5 ml of chloroform R. Evaporate the combined extracts to dryness on a water-bath, dissolve the residue in 20 ml of glacial acetic acid R1 and titrate with perchloric acid (0.05 mol/l) VS as described under "Non-aqueous titration", Method A (vol. 1, p. 131).

Each ml of perchloric acid (0.05 mol/l) VS is equivalent to 19.87 mg of $C_{18}H_{21}NO_3 \cdot H_3PO_4$. Calculate the content of codeine phosphate in the tablets either as hemihydrate or sesquihydrate, according to the label.

COLCHICINI COMPRESSI

Colchicine tablets

Category. Drug used for the treatment of gout.

Additional information. Strength in the current WHO Model list of essential drugs: 500 µg.

REQUIREMENTS

Complies with the monograph for "Tablets" (vol. 4, p. 26).

Colchicine tablets contain not less than 90.0% and not more than 110.0% of the amount of $C_{22}H_{25}NO_6$ stated on the label.

Identity tests

- *Either test A alone or tests B and C may be applied.*

- A. Triturate a quantity of the powdered tablets equivalent to about 20 mg of Colchicine with 20 ml of water. Allow the solids to settle and filter the supernatant liquid into a separatory funnel. Shake with 30 ml of chloroform R. Evaporate the chloroform layer to dryness using mild heat. Carry out the examination with the residue as described under "Spectrophotometry in the infrared region" (vol. 1, p. 40). The infrared absorption spectrum is concordant with the spectrum obtained from colchicine RS or with the *reference spectrum* of colchicine.
- B. The absorption spectrum of the solution obtained in the "Assay", when observed between 230 nm and 380 nm, exhibits two maxima at about 243 nm and 350 nm. The ratio of the absorbance at 243 nm to that at 350 nm is between 1.80 to 2.00.

C. Suspend a quantity of the powdered tablets in 1.5 ml of ethanol (~750 g/l) TS and filter. Place a few drops of the filtrate on a porcelain dish and evaporate to dryness on a water-bath. Mix the residue with 3 drops of sulfuric acid (~1760 g/l) TS; a lemon yellow colour is produced. Add 1 drop of nitric acid (~130 g/l) TS; the colour changes to greenish blue, turning rapidly to reddish and finally becoming yellowish. Following this add about 0.5 ml of sodium hydroxide (~200 g/l) TS; the colour turns to red.

Related substances. Carry out the test as described under "Thin-layer chromatography (vol. 1, p. 83), using a suitable aluminium oxide R as the coating substance containing a substance that fluoresces at about 254 nm and a mixture of 125 volumes of chloroform R, 100 volumes of acetone R and 2 volumes of ammonia (~260 g/l) TS as the mobile phase. Apply separately to the plate 2 µl of each of the following 2 solutions. For solution (A) shake a quantity of the powdered tablets equivalent to about 5 mg of Colchicine with 5 ml of chloroform R, filter and evaporate the filtrate to dryness in a current of air. Dissolve the residue as completely as possible in about 0.1 ml of ethanol (~750 g/l) TS. Allow to settle and use the supernatant liquid. For solution (B) dilute 1 volume of solution A to 20 volumes with ethanol (~750 g/l) TS. After removing the plate from the chromatographic chamber, allow it to dry in air 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.

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

Weigh and powder 20 tablets. To a quantity of the powder equivalent to about 0.5 g of Colchicine, add 10 ml of dehydrated ethanol R and shake for 30 minutes. Centrifuge, separate and wash the residue with dehydrated ethanol R. Combine the extract and washings and dilute to 50 ml with the same solvent. Measure the absorbance of a 1-cm layer at the maximum at about 350 nm, against a solvent cell containing dehydrated ethanol R.

Calculate the content of $C_{22}H_{25}NO_6$ using the absorptivity value of 42.5 ($A\ 1\%/1\ cm = 425$).

Uniformity of content.

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

Place 1 tablet in a centrifuge tube and add 10 ml of dehydrated ethanol R. Crush the tablet to a fine powder, shake for 30 minutes, centrifuge and wash the residue with dehydrated ethanol R. Combine the extract and washings and dilute to produce a solution of 0.01 mg per ml of dehydrated ethanol R. Measure the absorbance of a 1-cm layer at the maximum at about 350 nm, against a solvent cell containing dehydrated ethanol R.

Calculate the content of $C_{22}H_{25}NO_6$ using the absorptivity value of 42.5 ($A_{1\%/1\text{ cm}} = 425$). The tablets comply with the test for "Uniformity of content for single dose preparations" (vol. 4, p. 46).

DEXAMETHASONI COMPRESSI

Dexamethasone tablets

Category. Adrenal hormone.

Additional information. Strength in the current WHO Model list of essential drugs: 500 µg, 4 mg.

REQUIREMENTS

Complies with the monograph for "Tablets" (vol. 4, p. 26).

Dexamethasone tablets contain not less than 90.0% and not more than 110.0% of the amount of $C_{22}H_{29}FO_5$ stated on the label.

Identity tests

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

To a quantity of the powdered tablets equivalent to about 20 mg of Dexamethasone, add 50 ml of chloroform R and shake for 30 minutes. Filter, evaporate the filtrate to dryness and dry the residue at 105 °C for 2 hours. Use the residue for the following tests.

- Carry out the examination with the residue as described under "Spectrophotometry in the infrared region" (vol. 1, p. 40). The infrared absorption spectrum is concordant with the spectrum obtained from dexamethasone RS or with the *reference spectrum* of dexamethasone.
- Carry out the test as described under "Thin-layer chromatography (vol. 1, p. 83), using kieselguhr R1 as the coating substance and a mixture of 1 volume of formamide R and 9 volumes of acetone R to impregnate the plate, dipping it about 5 mm into the liquid. After the solvent has reached a height of at least 16 cm, remove the plate from the chromatographic chamber and allow it to stand at room temperature until the solvent has completely evaporated. Use the impregnated plate within 2 hours, carrying out the chromatography in the same direction as the impregnation. Use chloroform R as the mobile phase. Apply separately to the plate 2 µl of each of 3 solutions in a mixture of 9 volumes of chloroform R and 1 volume of methanol R containing (A) 2.5 mg of the residue per ml, (B) 2.5 mg of dexamethasone RS per ml and (C) a mixture of equal volumes of

solutions A and B. Develop the plate for a distance of 15 cm. After removing the plate from the chromatographic chamber, allow it to dry in air until the solvents have evaporated, heat at 120 °C for 15 minutes, and spray the hot plate with sulfuric acid/ethanol TS. Heat at 120 °C for a further 10 minutes, allow to cool, and examine the chromatogram in daylight and in ultraviolet light (365 nm).

The principal spot obtained with solution A corresponds in position, appearance, and intensity with that obtained with solution B. A single spot is obtained with solution C.

- C. Transfer a solution containing about 0.2 mg of the residue in 2.0 ml of ethanol (~750 g/l) TS to a stoppered test-tube, add 10 ml of phenylhydrazine/sulfuric acid TS, mix, heat in a water-bath at 60 °C for 20 minutes and cool immediately. The absorbance of a 1-cm layer at the maximum at about 423 nm is not less than 0.40.
- D. Transfer about 10 mg to a porcelain crucible, add 45 mg of magnesium oxide R and ignite until an almost white residue is obtained. Allow to cool, add 2.0 ml of water, 0.05 ml of phenolphthalein/ethanol TS and 1.0 ml of hydrochloric acid (~70 g/l) TS. Filter, to the filtrate add a freshly prepared mixture of 0.10 ml of sodium alzarinsulfonate (1 g/l) TS and 0.10 ml of zirconyl nitrate TS, mix, and allow to stand for 5 minutes. Repeat the test without the substance being examined. A yellow colour is produced in the solution of the substance being examined and the reagent blank turns red.

Assay. Weigh and powder 20 tablets. To a quantity of the powder equivalent to about 4.0 mg of Dexamethasone, add 15 ml of water and shake with four quantities, each of 25 ml, of chloroform R. Filter the chloroform layers through cotton-wool, previously washed with chloroform R, and add sufficient chloroform R to produce 200 ml. Transfer 10 ml of the resulting solution into a glass-stoppered 50-ml conical flask, carefully evaporate to dryness and dissolve the residue in 20 ml of dehydrated ethanol R. Add 2.0 ml of blue tetrazolium/ethanol TS, and displace the air in the flask with oxygen-free nitrogen R. Immediately add 2.0 ml of tetramethylammonium hydroxide/ethanol TS and again displace the air with oxygen-free nitrogen R. Stopper the flask, mix the contents by gentle swirling, and allow to stand for 1 hour in a water-bath at 30 °C. Cool rapidly, add sufficient aldehyde-free ethanol (~750 g/l) TS to produce 25 ml. and mix. Measure the absorbance of a 1-cm layer at the maximum at about 525 nm against a solvent cell containing a solution prepared by treating 10 ml of aldehyde-free ethanol (~750 g/l) TS in a similar manner.

Calculate the content of $C_{22}H_{29}FO_5$ by comparison with dexamethasone RS, similarly and concurrently examined.

Uniformity of content. Carry out the test as described under "High performance liquid chromatography" (vol. 3, p. 373), using a stainless steel column, length 20 cm, internal diameter 5 m, packed with silica gel (particle size of 5 µm) the surface of which has been modified with chemically bonded octadecyl silyl groups (Spherisorb ODS 1, is suitable).

As the mobile phase, use a mixture of 47 ml of methanol R with 53 ml of water.

For solution (A) use a mixture of 1 volume of a solution of 25 µg of dexamethasone RS per ml and 1 volume of a solution of 20 µg of hydrocortisone R in methanol R to serve as an internal standard. For solution (B) finely crush 1 tablet, add sufficient internal standard to produce a solution containing 25 µg of Dexamethasone per ml, shake for 10 minutes and filter through glass-fibre filter paper (Whatman GF/C is suitable).

Operate with a flow rate of 1.4 ml per minute. As a detector use an ultraviolet spectrophotometer at a wavelength of about 238 nm. Make 3 replicate injections of solution B, each of 20 µl, to determine the peak responses. The relative standard deviation of the peaks is not more than 1.0%. Inject 20 µl of each of solutions A and B. Measure the areas of the peak responses.

Calculate the content in % of $C_{22}H_{29}FO_5$. The tablets comply with the test for "Uniformity of content for single dose preparations" (vol. 4, p. 46).

DILOXANIDI FUROATIS COMPRESSI

Diloxanide furoate tablets

Category. Antiamoebic drug.

Additional information. Strength in the current WHO Model list of essential drugs: 500 mg.

REQUIREMENTS

Complies with the monograph for "Tablets" (vol. 4, p. 26).

Diloxanide furoate tablets contain not less than 95.0% and not more than 105.0% of the amount of $C_{14}H_{11}Cl_2NO_4$ stated on the label.

Identity tests

- *Either test A alone or tests B and C may be applied.*

To a quantity of the powdered tablets equivalent to about 0.2 g of Diloxanide furoate add 20 ml of chloroform R and shake. Filter, evaporate the filtrate to dryness and use the dried residue for the following tests.

- A. Carry out the examination with the residue as described under "Spectrophotometry in the infrared region" (vol. 1, p. 40). The infrared absorption spectrum is concordant with the spectrum obtained from diloxanide furoate RS or with the *reference spectrum* of diloxanide furoate.
- B. Melting temperature of the residue, about 115 °C.
- C. Carry out the combustion as described under "Oxygen flask method" (vol. 1, p. 125), using 20 mg of the residue and 10 ml of sodium hydroxide (1 mol/l) VS as the absorbing liquid. When the process is complete, acidify with nitric acid (~130 g/l); the solution yields reaction A, described under "General identification tests" as characteristic of chlorides (vol. 1, p. 112).

Related substances. Carry out the test as described under "Thin-layer chromatography" (vol. 1, p. 83), using silica gel R2 as the coating substance and a mixture of 96 volumes of dichloromethane R, and 4 volumes of methanol R as the mobile phase. Apply separately to the plate 5 µl of each of the following 2 solutions. For solution (A) shake a quantity of the powdered tablets equivalent to about 0.5 g of Diloxanide furoate with 5 ml of chloroform R, centrifuge and use the supernatant liquid. For solution (B) dilute 1 volume of solution A to 400 volumes of chloroform R. After removing the plate from the chromatographic chamber, allow it to dry in air 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. Weigh and powder 20 tablets. To a quantity of the powder equivalent to about 0.04 g of Diloxanide furoate add 150 ml of ethanol (~750 g/l) TS and shake for 30 minutes. Add sufficient ethanol (~750 g/l) TS to produce 200 ml, mix and filter. Dilute 10 ml of the filtrate to 250 ml with the same solvent. Measure the absorbance of a 1-cm layer at the maximum at about 258 nm against a solvent cell containing ethanol (~750 g/l) TS.

Calculate the content of $C_{14}H_{11}Cl_2NO_4$ using the absorptivity value of 70.5 ($A_{1\%}^{1\text{cm}} = 705$).

DOXYCYCLINI HYCLATIS COMPRESSI

Doxycycline hyclate tablets

Category. Antibacterial.

Storage. Doxycycline hyclate tablets should be kept in a tightly closed container.

Additional information. Strength in the current WHO Model list of essential drugs: 100 mg of doxycycline.

REQUIREMENTS

Doxycycline hyclate tablets contain not less than 90.0% and not more than 110.0% of the amount of $C_{22}H_{24}N_2O_8$ stated on the label.

Complies with the monograph for "Tablets" (vol. 4, p. 26).

Identity tests

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

A. Carry out the test as described under "Thin-layer chromatography (vol. 1, p. 83), using silica gel R3 as the coating substance. Adjust the pH of a solution of 0.1 g of disodium edetate R per ml to 9.0 with sodium hydroxide (~400 g/l) TS, and spray the solution evenly onto the plate. Allow the plate to dry in a horizontal position for not less than 1 hour. Just before use, dry the plate in an oven at 110 °C for 1 hour. Use a mixture of 6 volumes of water, 35 volumes of methanol R and 59 volumes of dichloromethane R as the mobile phase. Apply separately to the plate 1 µl of each of the following 3 solutions. For solution (A) shake a quantity of the powdered tablets equivalent to about 5 mg of Doxycycline hyclate with 5 ml of methanol R, filter, and dilute the filtrate to 10 ml with the same solvent and use the resulting solution. For solution (B) dissolve 5 mg of doxycycline hyclate RS in methanol R and dilute to 10 ml with the same solvent. For solution (C) dissolve 5 mg of doxycycline hyclate RS and 5 mg of tetracycline hydrochloride RS in methanol R and dilute to 10 ml with the same solvent. After removing the plate from the chromatographic chamber, allow it to dry in a current of air, and examine the chromatogram in ultraviolet light (365 nm).

The principal spot obtained with solution A corresponds in position, appearance, and intensity with that obtained with solution B. The test is valid only if the chromatogram obtained with solution C shows two clearly separated spots.

B. To a quantity of the powdered tablets equivalent to about 5 mg of Doxycycline hyclate add about 2 ml of sulfuric acid (~1760 g/l) TS; an intense yellow colour is produced.

To a quantity of the powdered tablets equivalent to about 0.1 g of Doxycycline hyclate add 10 ml of water, filter and use the filtrate for the following tests.

C. To 2.0 ml of the filtrate add 1 drop of ferric chloride (25 g/l) TS; a dark red-brown colour is produced.

D. To 1.0 ml of the filtrate add 5 drops of silver nitrate (40 g/l) TS; a white, curdy precipitate is formed which dissolves in 1.0 ml of ammonia (~100g/l) TS.

Light-absorbing impurities. To a quantity of the powdered tablets equivalent to about 0.10 g of Doxycycline hyclate add 10 ml of a mixture of 1 volume of hydrochloric acid (1 mol/l) VS and 99 volumes of methanol R, shake and filter, discarding the first two ml of filtrate. Measure the absorbance of a 1-cm layer at 490 nm; the absorbance does not exceed 0.2.

Assay.

Either method A or method B may be applied.

A. Weigh and powder 20 tablets. To a quantity of the powder equivalent to about 50 mg, accurately weighed, add 50 ml of dimethylformamide R and shake for 1 hour. Centrifuge, and carry out the assay with the supernatant liquid as described under "Microbiological assay of antibiotics" (vol. 1, p. 145), using *Bacillus cereus* (NCTC 10320 or ATCC 11778) as the test organism, culture medium Cm10 with a final pH of 6.6, potassium dihydrogen phosphate (13.6 g/l) TS as the buffer, an appropriate concentration of Doxycycline (usually between 0.2 and 2.0 IU per ml), and an incubation temperature of 35–39 °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%.

The upper fiducial limit of error is not less than 97.0% and the lower fiducial limit of error is not more than 110.0% of the content stated on the label expressed in mg, taking 870 IU found to be equivalent to 1 mg of doxycycline (C₂₂H₂₄N₂O₈).

B. Carry out the test as described under "High performance liquid chromatography" (vol. 3, p. 373), using a column, length 25 cm, internal diameter 4.6 mm, packed with styrene-divinylbenzene copolymer (particle size 8–10 µm from a commercial source, is suitable).

As the mobile phase, use the following solution: Transfer 60.0 g of *tert*-butanol R, with the aid of 200 ml of water to a 1000-ml volumetric flask. Add 400 ml of buffer borate pH 8.0, TS, 50 ml of a solution of 10 mg of tetrabutylammonium hydrogen sulfate R per ml adjusted to pH 8.0 with sodium hydroxide (~80 g/l) TS and 20 ml of sodium edetate (20 g/l) TS adjusted to pH 8.0 with sodium hydroxide (~80 g/l) TS. Dilute to 1000 ml with water.

For solution (A) use 0.80 mg of Doxycycline hyclate per ml of hydrochloric acid (0.01 mol/l) VS, for solution (B) 0.80 mg of doxycycline hyclate RS per ml of hydrochloric acid (0.01 mol/l) VS, for solution (C) 0.80 mg of 6-epidoxycycline hydrochloride RS per ml of hydrochloric acid (0.01 mol/l) VS, for solution (D) 0.80 mg of metacycline hydrochloride RS per ml of hydrochloric acid (0.01 mol/l) VS, for solution (E) mix 4.0 ml of solution B with 1.5 ml of solution C and 1.0 ml of solution D and dilute to 25 ml with hydrochloric

acid (0.01 mol/l) VS, and for solution (F) mix 2.0 ml of solution C and 2.0 ml of solution D and dilute to 100 ml with hydrochloric acid (0.01 mol/l) VS.

Operate with a flow rate of 1.0 ml per minute. Use an injector with a fixed loop of 20 μ l, as detector an ultraviolet spectrophotometer at a wavelength of about 254 nm with an electronic integrator. Inject solution E, adjust the attenuation to obtain peaks with a height corresponding to at least half the full-scale deflection. The test is not valid unless the resolution between the first peak (metacycline) and the second peak (6-epidoxycycline) is not less than 1.25 and the resolution between the second peak and the third peak (doxycycline) is not less than 2.0. Adjust the *tert*-butanol R content in the mobile phase, if necessary. The test is not valid unless the symmetry factor for the third peak is not more than 1.25.

Inject solution B six times, the test is not valid unless the relative standard deviation of the peak area for doxycycline is not greater than 1.0%. If necessary adjust the integrator parameters. Inject alternately solutions A and B.

Calculate the content in % of $C_{22}H_{24}N_2O_8$.

Dissolution test. (See introduction).

ERYTHROMYCINI ETHYLSUCCINATIS COMPRESSI

Erythromycin ethylsuccinate tablets

Category. Antibacterial.

Storage. Erythromycin ethylsuccinate tablets should be kept in a tightly closed container.

Additional information. Strength in the current WHO Model list of essential drugs: 250 mg of erythromycin.

REQUIREMENTS

Erythromycin ethylsuccinate tablets contain not less than 90.0% and not more than 110.0% of the amount of erythromycin $C_{37}H_{67}NO_{13}$ stated on the label.

Complies with the monograph for "Tablets" (vol. 4, p. 26).

Identity tests

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

To a quantity of the powdered tablets equivalent to about 0.25 g of Erythromycin ethylsuccinate, add 20 ml of chloroform R and shake. Filter, evaporate the filtrate to dryness and use the dried residue for tests A, C and D.

A. Carry out the examination with the residue as described under "Spectrophotometry in the infrared region" (vol. 1, p. 40). The infrared absorption spectrum is concordant with the spectrum obtained from erythromycin ethylsuccinate RS or with the *reference spectrum* of erythromycin ethylsuccinate:

B. Carry out the test as described under "Thin-layer chromatography (vol. 1, p. 83), using silica gel R1 as the coating substance and a mixture of 85 volumes of methanol R and 15 volumes of chloroform R as the mobile phase. Apply separately to the plate 10 μ l of each of the following 2 solutions. For solution (A) shake a quantity of the powdered tablets equivalent to about 30 mg of Erythromycin ethylsuccinate with 10 ml of methanol R and shake by mechanical means for 30 minutes. Centrifuge a portion of this mixture and use the clear supernatant liquid. For solution (B) use 3 mg of erythromycin ethylsuccinate RS per ml of methanol R. After removing the plate from the chromatographic chamber, allow it to dry in a current of air, and spray with a mixture of 90 volumes of dehydrated ethanol R, 5 volumes of anisaldehyde R and 5 volumes of sulfuric acid (~1760 g/l) TS. Heat the plate at 100 °C for 10 minutes and examine the chromatogram in daylight.

The principal spot obtained with solution A corresponds in position, appearance, and intensity with that obtained with solution B.

C. To 5 mg of the residue, add about 2 ml of sulfuric acid (~1760 g/l) TS and shake gently; a reddish brown colour is produced.

D. Dissolve about 3 mg of the residue in 2.0 ml of acetone R and add about 2 ml of hydrochloric acid (~420 g/l) TS; an orange colour is produced, which changes to orange-red and finally to violet-red. Add 2.0 ml of chloroform R and shake; the chloroform layer turns to blue.

Assay. Weigh and powder 20 tablets. To a quantity of the powder equivalent to about 50 mg, accurately weighed, add 50 ml of methanol R, shake and filter. Carry out the assay with the filtrate as described under "Microbiological assay of antibiotics" (vol. 1, p. 145), using *Bacillus pumilus* (NCTC 8241 or ATCC 14884) as the test organism, culture medium Cm1 with a final pH of 8.0–8.1, sterile phosphate buffer, pH 8.0 TS1 or TS2, an appropriate concentration of Erythromycin (usually between 5 and 15 IU per ml), and an incubation temperature of 35–39 °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%.

The upper fiducial limit of error is not less than 90.0% and the lower fiducial limit of error is not more than 120.0% of the content stated on the label, expressed in mg, taking 920 IU found to be equivalent to 1 mg of erythromycin (C₃₇H₆₇NO₁₃).

Dissolution test. (See introduction).

ERYTHROMYCINI STEARATIS COMPRESSI

Erythromycin stearate tablets

Category. Antibacterial.

Storage. Erythromycin stearate tablets should be kept in a tightly closed container.

Additional information. Strength in the current WHO Model list of essential drugs: 250 mg of erythromycin.

REQUIREMENTS

Erythromycin stearate tablets contain not less than 90.0% and not more than 110.0% of the amount of erythromycin C₃₇H₆₇NO₁₃ stated on the label.

Complies with the monograph for "Tablets" (vol. 4, p. 26).

Identity tests

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

- A. To a quantity of the powdered tablets equivalent to about 0.2 g of Erythromycin stearate, add 20 ml of water and shake. Decant the supernatant liquid and discard. Add 10 ml of methanol R to the residue and shake, filter and evaporate to dryness. Carry out the examination with the dried residue as described under "Spectrophotometry in the infrared region" (vol. 1, p. 40). The infrared absorption spectrum is concordant with the spectrum obtained from erythromycin stearate RS or with the *reference spectrum* of erythromycin stearate.
- B. Carry out the test as described under "Thin-layer chromatography (vol. 1, p. 83), using silica gel R4 as the coating substance and a mixture of 85 volumes of methanol R and 15 volumes of chloroform R as the mobile phase. Apply separately to the plate 20 µl of each of the following 2 solutions. For solution (A) shake a

quantity of the powdered tablets equivalent to about 0.05 g of Erythromycin stearate with 10 ml of methanol R and shake by mechanical means for 30 minutes. Centrifuge a portion of this mixture and use the clear supernatant liquid. For solution (B) use 5 mg of erythromycin stearate RS per ml of methanol R. After removing the plate from the chromatographic chamber, allow it to dry in a current of air, and spray with dichlorofluorescein TS. Heat the plate at 100 °C for 10 minutes and examine the chromatogram in ultraviolet light (365 nm).

The principal spot obtained with solution A corresponds in position, appearance, and intensity with that obtained with solution B.

Then spray with a mixture of 90 volumes of dehydrated ethanol R, 5 volumes of anisaldehyde R and 5 volumes of sulfuric acid (~1760 g/l) TS. Heat the plate at 100 °C for 10 minutes and examine the chromatogram in daylight.

The principal spot obtained with solution A corresponds in position, appearance, and intensity with that obtained with solution B.

C. To a quantity of the powdered tablets equivalent to about 10 mg of Erythromycin stearate add 2.0 ml of acetone R and about 2 ml of hydrochloric acid (~420 g/l) TS and shake; a pale orange colour is produced, which changes to red or violet-red. Add 2.0 ml of chloroform R and shake; the chloroform layer acquires a violet colour.

D. Shake a quantity of the powdered tablets equivalent to about 0.1 g of Erythromycin stearate with 10 ml of chloroform R, filter, and evaporate the filtrate to dryness on a water-bath. Gently heat the residue with 10 ml of water and 5 ml of hydrochloric acid (~70 g/l) TS until the solution boils; oily globules rise to the surface. Cool, remove the fatty layer, and heat it with 3.0 ml of sodium hydroxide (0.1 mol/l) VS. Allow to cool; the solution sets to a gel. Add 10 ml of hot water, shake, heat the mixture for 2-3 minutes and shake again; the solution froths. To 1.0 ml of the resulting solution add 2.0 ml of calcium chloride (55 g/l) TS; a granular precipitate is produced, which is insoluble in hydrochloric acid.

Assay. Weigh and powder 20 tablets. To a quantity of the powder equivalent to about 50 mg, accurately weighed, add 50 ml of methanol R, shake and filter. Carry out the assay with the filtrate as described under "Microbiological assay of antibiotics" (vol. 1, p. 145), using *Bacillus pumilus* (NCTC 8241 or ATCC 14884) as the test organism, culture medium Cm1 with a final pH of 8.0-8.1, sterile phosphate buffer, pH 8.0 TS1 or TS2, an appropriate concentration of Erythromycin (usually between 5 and 25 IU per ml), and an incubation temperature of 35-39 °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%.

The upper fiducial limit of error is not less than 90.0% and the lower fiducial limit of error is not more than 120.0% of the content stated on the label, expressed in mg, taking 920 IU found to be equivalent to 1 mg of erythromycin ($C_{37}H_{67}NO_{13}$).

Dissolution test. (See introduction).

ETHAMBUTOLI HYDROCHLORIDI COMPRESSI

Ethambutol hydrochloride tablets

Category. Antituberculosis drug.

Additional information. Strength in the current WHO Model list of essential drugs: 100–400 mg.

REQUIREMENTS

Complies with the monograph for "Tablets" (vol. 4, p. 26).

Ethambutol hydrochloride tablets contain not less than **95.0%** and not more than **105.0%** of the amount of $C_{10}H_{24}N_2O_2 \cdot 2HCl$ stated on the label.

Identity tests

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

To a quantity of the powdered tablets equivalent to about 0.1 g of Ethambutol hydrochloride add 10 ml of methanol R and shake. Filter the extract and evaporate to dryness. Use the residue for tests A and C.

A. Carry out the examination with the residue as described under "Spectrophotometry in the infrared region" (vol. 1, p. 40). The infrared absorption spectrum is concordant with the spectrum obtained from ethambutol hydrochloride RS or with the *reference spectrum* of ethambutol hydrochloride.

B. Carry out the test as described under "Thin-layer chromatography (vol. 1, p. 83), using silica gel R1 as the coating substance and a mixture of 1.5 volumes of ammonia (~260 g/l) TS and 100 volumes of methanol R as the mobile phase. Apply separately to the plate 10 μ l of each of the following 2 solutions. For solution (A) shake a quantity of the powdered tablets equivalent to about 10 mg of Ethambutol hydrochloride with 10 ml of water, filter and use the filtrate. For solution (B) use 1.0 mg of ethambutol hydrochloride RS per ml. After

removing the plate from the chromatographic chamber, allow it to dry in air, and expose it to the vapour of iodine R until spots appear. Examine the chromatogram in daylight.

The principal spot obtained with solution A corresponds in position, appearance, and intensity with that obtained with solution B.

C. The residue yields reaction A described under "General identification tests" as characteristic of chlorides (vol. 1, p. 112).

Aminobutanol. Carry out the test as described under "Thin-layer chromatography (vol. 1, p. 83), using silica gel R1 as the coating substance and a mixture of 55 volumes of ethyl acetate R, 35 volumes of glacial acetic acid R, 5 volumes of hydrochloric acid (~420 g/l) TS and 1 volume of water as the mobile phase. Apply separately to the plate 2 µl of each of the following 2 solutions. For solution (A) shake a quantity of the powdered tablets equivalent to about 0.5 g of Ethambutol hydrochloride with 10 ml of methanol R for 5 minutes, filter and use the filtrate. For solution (B) use 0.5 mg of aminobutanol R per ml of methanol R. After removing the plate from the chromatographic chamber, allow it to dry in air, heat at 105 °C for 5 minutes, cool, spray with triketohydrindene/cadmium TS and heat again at 90 °C for 5 minutes. Examine the chromatogram in daylight.

Any spot obtained with solution A corresponding to aminobutanol is not more intense than that obtained with solution B.

Assay. Weigh and powder 20 tablets. To a quantity of the powder equivalent to about 0.2 g of Ethambutol hydrochloride add 10 ml of sodium hydroxide (~80 g/l) TS and extract with 5 portions, each of 20 ml of chloroform R. Evaporate the combined extracts to a volume of about 25 ml, filter, add 100 ml of glacial acetic acid R1, and titrate with perchloric acid (0.1 mol/l) VS as described under "Non-aqueous titration", Method A (vol. 1, p. 131), using 1-naphtholbenzein/acetic acid TS as indicator.

Each ml of perchloric acid (0.1 mol/l) VS is equivalent to 13.86 mg of $C_{10}H_{24}N_2O_2 \cdot 2HCl$.

Dissolution test. (See introduction).

IBUPROFENI COMPRESSI

Ibuprofen tablets

Category. Non-steroidal anti-inflammatory drug.

Additional information. Strength in the current WHO Model list of essential drugs: 200 mg.

REQUIREMENTS

Complies with the monograph for "Tablets" (vol. 4, p. 26).

Ibuprofen tablets contain not less than 90.0% and not more than 110.0% of the amount of $C_{13}H_{18}O_2$ stated on the label.

Identity tests

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

To a quantity of the powdered tablets equivalent to about 0.8 g of Ibuprofen add 20 ml of acetone R, filter and allow the filtrate to evaporate without heating. To the residue add 10 ml of acetone R, allow to crystallize, separate the crystals, dry in air and use the dried crystals for the following tests.

- Carry out the examination with the dried crystals as described under "Spectrophotometry in the infrared region" (vol. 1, p. 40). The infrared absorption spectrum is concordant with the spectrum obtained from ibuprofen RS or with the *reference spectrum* of ibuprofen.
- Dissolve 25 mg of the dried crystals in sufficient sodium hydroxide (0.1 mol/l) VS to produce 100 ml. The absorption spectrum of the resulting solution, when observed between 230 nm and 350 nm, exhibits maxima at about 265 nm and 273 nm, minima at about 245 nm and 271 nm, and a shoulder at about 259 nm.
- See the test described below under "Related substances". The principal spot obtained with solution A corresponds in position, appearance, and intensity with that obtained with solution B.
- Melting temperature of the dried crystals, about 76 °C.

Related substances. Carry out the test as described under "Thin-layer chromatography" (vol. 1, p. 83), using silica gel R3 as the coating substance and a mixture of 15 volumes of hexane R, 5 volumes of ethyl acetate R, and 1 volume of glacial acetic acid R as the mobile phase. Apply separately to the plate 5 µl of each of the following 3 solutions. For solution (A) shake a quantity of the powdered tablets equivalent to about 0.2 g of Ibuprofen with three 10-ml quantities of chloroform R, filter, evaporate the combined filtrates to a volume of about 1 ml and add sufficient chloroform R to produce 2 ml. For solution (B) use 0.1 g of ibuprofen RS per ml of chloroform R. For solution (C) dilute 1 volume of solution A to 100 volumes with chloroform R. After removing the plate from the chromatographic chamber, allow it to dry in air, spray very lightly with a solution of 10 mg of potassium permanganate R per ml of sulfuric acid (~100 g/l) TS. Heat again at 120 °C for 20 minutes and examine the chromatogram in ultraviolet light (365 nm).

Any spot obtained with solution A, other than the principal spot, is not more intense than that obtained with solution C.

Assay. Weigh and powder 20 tablets. To a quantity of the powder equivalent to about 0.5 g of Ibuprofen add 60 ml of chloroform R and shake for 15 minutes. Filter through a fine glass microfibre paper (Whatman GF/F is suitable) under reduced pressure. Wash the residue with 2 quantities, each of 20 ml of chloroform R, and evaporate the combined filtrates just to dryness in a current of air. Dissolve the residue in 100 ml of neutralized ethanol TS and titrate with sodium hydroxide (0.1 mol/l) VS determining the endpoint potentiometrically.

Each ml of sodium hydroxide (0.1 mol/l) VS is equivalent to 20.63 mg of $C_{13}H_{18}O_2$.

Dissolution test. (See introduction).

INDOMETACINI COMPRESSI

Indometacin tablets

Category. Non-steroidal anti-inflammatory drug.

Additional information. Strength in the current WHO Model list of essential drugs: 25 mg.

REQUIREMENTS

Complies with the monograph for "Tablets" (vol. 4, p. 26).

Indometacin tablets contain not less than **90.0%** and not more than **110.0%** of the amount of $C_{19}H_{16}ClNO_4$ stated on the label.

Identity tests

- *Either test A alone or tests B and C may be applied.*

A. To a quantity of the powdered tablets equivalent to about 0.1 g of Indometacin add 5 ml of chloroform R and shake. Filter and evaporate the filtrate to dryness. Dry the residue at 70 °C under reduced pressure (not exceeding 0.6 kPa or 5 mm of mercury). Carry out the examination with the residue as described under

"Spectrophotometry in the infrared region" (vol. 1, p. 40). The infrared absorption spectrum is concordant with the spectrum obtained from indometacin RS or with the *reference spectrum* of indometacin.

- B. To a quantity of the powdered tablets equivalent to about 0.05 g of Indometacin add 60 ml of ethanol (~750 g/l) TS and shake. Allow to stand for 10 minutes, shake again and dilute with sufficient ethanol (~750 g/l) TS to produce 100 ml. Filter, discard the first 10 ml of filtrate, then dilute 5 ml of the filtrate to 100 ml with the same solvent. The absorption spectrum of the resulting solution, when observed between 300 nm and 350 nm, exhibits a maximum at about 318 nm.
- C. To a quantity of the powdered tablets equivalent to about 25 mg add 10 ml of water, 2 drops of sodium hydroxide (~200 g/l) TS, shake and filter. To the filtrate add 1.0 ml of sodium nitrite (10 g/l) TS, allow to stand for 5 minutes and cautiously add about 0.5 ml of hydrochloric acid (~250 g/l) TS; a green colour is produced.

Related substances. Carry out the test as described under "Thin-layer chromatography (vol. 1, p. 83), using silica gel R2 as the coating substance and preparing a slurry in sodium dihydrogen phosphate (45 g/l) TS. As the mobile phase, use a mixture of 7 volumes of ether R and 3 volumes of light petroleum R1. Apply separately to the plate 5 µl of each of the following 2 solutions. For solution (A) shake a quantity of the powdered tablets equivalent to about 0.1 g of Indometacin with 5 ml of chloroform R, filter, and use the filtrate. For solution (B) dilute 1 volume of solution A to 200 volumes with chloroform R. After removing the plate from the chromatographic chamber, allow it to dry in air, 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. Weigh and powder 20 tablets. To a quantity of the powder equivalent to about 0.05 g of Indometacin add 10 ml of water and allow to stand for 15 minutes, swirling occasionally. Add 75 ml of methanol R, shake well, add sufficient methanol R to produce 100 ml and filter. To 5 ml of the filtrate add a mixture of equal volumes of methanol R and phosphate buffer pH 7.2, TS to produce 100 ml. Measure the absorbance of a 1-cm layer at the maximum at about 318 nm, against a solvent cell containing the above solvent mixture.

Calculate the content of $C_{19}H_{16}ClNO_4$ using the absorptivity value of 19.3 ($A_{1\%}^{1\text{cm}} = 193$).

Dissolution test. (See introduction).

ISONIAZIDI COMPRESSI

Isoniazid tablets

Category. Antituberculosis drug.

Additional information. Strength in the current WHO Model list of essential drugs: 100–300 mg.

REQUIREMENTS

Complies with the monograph for "Tablets" (vol. 4, p. 26).

Isoniazid tablets contain not less than **95.0%** and not more than **105.0%** of the amount of $C_6H_7N_3O$ stated on the label.

Identity tests

• *Either test A alone or tests B and C may be applied.*

A. To a quantity of the powdered tablets equivalent to about 0.1 g of Isoniazid add 10 ml of ethanol (~750 g/l) TS and shake for 15 minutes. Centrifuge, and decant the supernatant liquid. Extract the remaining liquid with two further 10-ml quantities of ethanol (~750 g/l) TS and evaporate the combined extracts to dryness. Carry out the examination with the residue as described under "Spectrophotometry in the infrared region" (vol. 1, p. 40). The infrared absorption spectrum is concordant with the spectrum obtained from isoniazid RS or with the *reference spectrum* of isoniazid.

B. To a quantity of the powdered tablets equivalent to about 0.1 g of Isoniazid add 2.0 ml of water, shake and filter. Then add a mixture composed of 1.0 ml of silver nitrate (40 g/l) TS and 1.0 ml of ammonia (~100 g/l) TS; bubbles of nitrogen evolve, the mixture turns from yellow to black and a metallic silver mirror appears on the sides of the test-tube.

C. See the test described below under "Related substances". The principal spot obtained with solution A corresponds in position, appearance, and intensity with that obtained with solution B.

Related substances. Carry out the test as described under "Thin-layer chromatography (vol. 1, p. 83), using silica gel R2 as the coating substance and a mixture of equal volumes of acetone R and methanol R as the mobile phase. Apply separately to the plate 10 μ l of each of the 3 following solutions. For solution (A) shake a quantity of the powdered tablets equivalent to about 0.1 g of Isoniazid with 10 ml of methanol R, filter, and use the filtrate. For solution (B) use 10 mg of isoniazid RS per ml of methanol R. For solution (C) dilute 1 volume of

solution A to 100 volumes with methanol R. After removing the plate from the chromatographic chamber, allow it to dry in air, 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 C.

Assay. Weigh and powder 20 tablets. Dissolve a quantity of the powdered tablets equivalent to about 0.4 g of Isoniazid as completely as possible in water, filter and wash the residue with sufficient water to produce 250 ml. Place 50 ml of the resulting solution in a titration vessel, add 50 ml of water, 20 ml of hydrochloric acid (~250 g/l) TS and 0.2 g of potassium bromide R, and titrate with potassium bromate (0.0167 mol/l) VS as described under "Nitrite titration" (vol. 1, p. 133).

Each ml of potassium bromate (0.0167 mol/l) VS is equivalent to 3.429 mg of $C_6H_7N_3O$.

Dissolution test. (See introduction).

MORPHINI SULFATIS COMPRESSI

Morphine sulfate tablets

Category. Opioid analgesic.

Additional information. Strength in the current WHO Model list of essential drugs: 10 mg.

REQUIREMENTS

Complies with the monograph for "Tablets" (vol. 4, p. 26).

Morphine sulfate tablets contain not less than **90.0%** and not more than **110.0%** of the amount of $(C_{17}H_{19}NO_3)_2 \cdot H_2SO_4 \cdot 5H_2O$ stated on the label.

Identity tests

- *Either tests A and D or tests B, C and D may be applied.*
- A. To a quantity of the powdered tablets equivalent to about 0.1 g of Morphine sulfate add 10 ml of ethanol (~750 g/l) TS and shake for 15 minutes. Centrifuge, and decant the supernatant liquid. Extract the remaining

liquid with two further 10-ml quantities of ethanol (~750 g/l) TS and evaporate the combined extracts to dryness. Carry out the examination with the residue as described under "Spectrophotometry in the infrared region" (vol. 1, p. 40). The infrared absorption spectrum is concordant with the spectrum obtained from morphine sulfate RS or with the *reference spectrum of morphine sulfate*.

B. To a quantity of the powdered tablets equivalent to about 20 mg of Morphine sulfate add 5 ml of water, shake and filter. To the filtrate add 0.05 ml of ferric chloride (25 g/l) TS; a blue colour is produced.

C. To a quantity of the powdered tablets equivalent to about 20 mg of Morphine sulfate add 5 ml of sulfuric acid (0.05 mol/l) VS, shake and filter. To the filtrate add 0.5 ml of a saturated solution of potassium iodate R; an amber colour is produced which reaches maximum intensity after about 5 minutes. Add 0.5 ml of ammonia (~260 g/l) TS; the colour darkens almost to black.

D. To a quantity of the powdered tablets equivalent to about 20 mg of Morphine sulfate add 5 ml of water, shake and filter. The filtrate yields the reactions described under "General identification tests" as characteristic of sulfates (vol. 1, p. 115).

Assay. Weigh and powder 20 tablets. To a quantity of the powdered tablets equivalent to about 0.4 g of Morphine sulfate add 25 ml of water, 5 ml of sodium hydroxide (1 mol/l) VS and 1 g of ammonium sulfate R, and swirl to dissolve. Add 20 ml of ethanol (~750 g/l) TS and extract with successive quantities of 40 ml, 20 ml, 20 ml and 20 ml of a mixture of 3 volumes of chloroform R and 1 volume of ethanol (~750 g/l) TS. Wash each extract with the same 5 ml of water, filter, and evaporate the solvent. Dissolve the residue in 10 ml of hydrochloric acid (0.05 mol/l) VS, boil, cool, add 15 ml of water and titrate the excess of acid with sodium hydroxide (0.05 mol/l) VS, using methyl red/ethanol TS as indicator.

Each ml of hydrochloric acid (0.05 mol/l) VS is equivalent to 18.97 mg of $(C_{17}H_{19}NO_3)_2 \cdot H_2SO_4 \cdot 5H_2O$.

PETHIDINI HYDROCHLORIDI COMPRESSI

Pethidine hydrochloride tablets

Category. Opioid analgesic.

Additional information. Strength in the current WHO Model list of essential drugs: 50 mg, 100 mg.

REQUIREMENTS

Complies with the monograph for "Tablets" (vol. 4, p. 26).

Pethidine hydrochloride tablets contain not less than **90.0%** and not more than **110.0%** of the amount of $C_{15}H_{21}NO_2 \cdot HCl$ stated on the label.

Identity tests

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

A. To a quantity of the powdered tablets equivalent to about 0.05 g of Pethidine hydrochloride add 20 ml of chloroform R, shake and filter. Evaporate the filtrate to dryness and dry the residue under reduced pressure (not exceeding 0.6 kPa or 5 mm of mercury). Carry out the examination with the residue as described under "Spectrophotometry in the infrared region" (vol. 1, p. 40). The infrared absorption spectrum is concordant with the spectrum obtained from pethidine hydrochloride RS or with the *reference spectrum* of pethidine hydrochloride.

B. To a quantity of the powdered tablets equivalent to about 0.2 g of Pethidine hydrochloride add 20 ml of water, shake and filter. To 5 ml of the filtrate (keep the remaining filtrate for tests C and D) add 5 ml of trinitrophenol/ethanol TS and shake; a yellow, crystalline precipitate is produced. Filter, wash with water and dry the crystals at 105 °C for 2 hours; melting temperature, about 190 °C.

C. Evaporate 1 ml of the filtrate from test B to dryness on a water-bath, dissolve the residue in 1 ml of formaldehyde/sulfuric acid TS and heat cautiously; the colour of the solution turns to pink changing to violet-red and showing a red fluorescence when held in front of a strong light.

D. Dilute 5 ml of the filtrate from test B with 5 ml of water; it yields the reactions described under "General identification tests" as characteristic of chlorides (vol. 1, p. 112).

Related substances. Carry out the test as described under "Thin-layer chromatography (vol. 1, p. 83), using kieselguhr R1 as the coating substance and a mixture of 9 volumes of acetone R and 1 volume of 2-phenoxyethanol R and to impregnate the plate, dipping it about 5 mm into the liquid. After the solvent has reached a height of at least 16 cm, remove the plate from the chromatographic chamber and dry it in a current of air. Use the impregnated plate immediately, carrying out the chromatography in the same direction as the impregnation.

Shake together 100 volumes of light petroleum R1, 8 volumes of 2-phenoxyethanol R and 1 volume of diethylamine R, allow to settle, and use this solution as the mobile phase. Apply separately to the plate 5 µl of each of the following 2 solutions. For solution (A) shake a quantity of the powdered tablets equivalent to about

0.1 g of Pethidine hydrochloride with 5 ml of water, filter, shake the filtrate with 0.5 ml of sodium hydroxide (~200 g/l) TS and 2 ml of ether R, allow the layers to separate and use the upper layer. For solution (B) dilute 0.5 ml of solution A to 50 ml with ether R. After removing the plate from the chromatographic chamber, allow it to dry in air for 10 minutes, return the plate to the chromatographic chamber and repeat the development. Remove the plate, allow it to dry in air for 10 minutes and spray with dichlorofluorescein TS. Allow to stand for 5 minutes and spray with water until the background is white to pale yellow. Examine the chromatogram in daylight.

The chromatograms show red to orange spots. Any spot obtained with solution A, other than the principal spot, is not more intense than that obtained with solution B. Examine the chromatogram without delay in ultraviolet light (365 nm). The chromatograms show spots with intense yellow fluorescence. Any spot obtained with solution A, other than the principal spot, is not more intense than that obtained with solution B.

Assay. Weigh and powder 20 tablets. To a quantity of the powdered tablets equivalent to about 0.5 g of Pethidine hydrochloride add 40 ml of water, 2.0 ml of sodium hydroxide (~200 g/l) TS and extract immediately with quantities of 25 ml, 10 ml and 10 ml of chloroform R. Wash each extract with the same 15 ml of water and filter into a dry flask. Titrate the combined extracts, which should be clear and free from droplets of water, with perchloric acid (0.05 mol/l) VS as described under "Non-aqueous titration", Method A (vol. 1, p. 131), using 0.15 ml of 1-naphtholbenzein/acetic acid TS as indicator.

Each ml of perchloric acid (0.05 mol/l) VS is equivalent to 14.19 mg of $C_{15}H_{21}NO_2 \cdot HCl$.

PHENOBARBITALI COMPRESSI

Phenobarbital tablets

Category. Antiepileptic drug.

Additional information. Strength in the current WHO Model list of essential drugs: 15–100 mg.

REQUIREMENTS

Complies with the monograph for "Tablets" (vol. 4, p. 26).

Phenobarbital tablets contain not less than 90.0% and not more than 110.0% of the amount of $C_{12}H_{12}N_2O_3$ stated on the label.

Identity tests

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

To a quantity of the powdered tablets equivalent to about 0.4 g of Phenobarbital add 10 ml of dehydrated ethanol R, shake and filter. Evaporate the filtrate to dryness and dry the residue at 105 °C for 1 hour. Use the residue for the following tests.

- Carry out the examination with the residue as described under "Spectrophotometry in the infrared region" (vol. 1, p. 40). The infrared absorption spectrum is concordant with the spectrum obtained from phenobarbital RS or with the *reference spectrum* of phenobarbital. If the spectra obtained are not concordant, heat the residue in a sealed tube at 105 °C for 1 hour and prepare a new spectrum of the residue.
- Melting temperature of the residue, about 174 °C.
- Dissolve 20 mg of the residue in 5 ml of methanol R, add 1 drop of cobalt(II) chloride (30 g/l) TS and 3–4 drops of ammonia (~100 g/l) TS; a violet colour is produced.
- To 0.20 g of the residue add about 2 ml of sulfuric acid (~1760 g/l) TS, 20 mg of sodium nitrate R and allow to stand for 30 minutes; a yellow colour is produced.

Assay. Weigh and powder 20 tablets. To a quantity of the powdered tablets equivalent to about 0.2 g of Phenobarbital add 40 ml of methanol R and 15 ml of a freshly prepared solution of 30 mg of anhydrous sodium carbonate R per ml. Titrate with silver nitrate (0.1 mol/l) VS, determining the endpoint potentiometrically.

Each ml of silver nitrate (0.1 mol/l) VS is equivalent to 23.22 mg of $C_{12}H_{12}N_2O_3$.

Disintegration test. Complics with the test for "Disintegration test for tablets and capsules" (volume 4, p. 40).
Time period: 30 minutes.

PHENYTOINI NATRICI COMPRESSI

Phenytoin sodium tablets

Category. Antiepileptic drug.

Additional information. Strength in the current WHO Model list of essential drugs: 25 mg, 50 mg, 100 mg.

REQUIREMENTS

Complies with the monograph for "Tablets" (vol. 4, p. 26).

Phenytoin sodium tablets contain not less than **90.0%** and not more than **110.0%** of the amount of $C_{15}H_{11}N_2NaO_2$ stated on the label.

Identity tests

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

To a quantity of the powdered tablets equivalent to about 0.1 g of Phenytoin sodium add 20 ml of water, shake and filter. Acidify the filtrate with hydrochloric acid (~70 g/l) TS and extract with chloroform R. Wash the chloroform extract with water, dry with anhydrous sodium sulfate R and evaporate to dryness. Use the residue for tests A and B.

A. Carry out the examination with the residue as described under "Spectrophotometry in the infrared region" (vol. 1, p. 40). The infrared absorption spectrum is concordant with the spectrum obtained from phenytoin RS or with the *reference spectrum* of phenytoin.

B. Carry out the test as described under "Thin-layer chromatography (vol. 1, p. 83), using silica gel R4 as the coating substance and a mixture of 1 volume of acetone R and 9 volumes of chloroform R as the mobile phase. Apply separately to the plate 10 μ l of each of the following 2 solutions in chloroform R. For solution (A) use 1 mg of the residue per ml. For solution (B) use 1 mg of phenytoin RS per ml. After removing the plate from the chromatographic chamber, allow it to dry and examine the chromatogram in ultraviolet light (254 nm).

The principal spot obtained with solution A corresponds in position, appearance, and intensity with that obtained with solution B.

C. To a quantity of the powdered tablets equivalent to about 40 mg of Phenytoin sodium add 2.0 ml of ammonia (~100 g/l) TS and heat until boiling begins. Add 1 drop of copper(II) sulfate (160 g/l) TS and shake; a blue-violet solution with a blue-green precipitate is produced. Allow to stand for 3 minutes, filter and wash with water; pink needles remain on the filter.

D. To a quantity of the powdered tablets equivalent to about 40 mg of Phenytoin sodium add 5 ml of water, shake and filter. The filtrate yields reaction B described under "General identification tests" as characteristic of sodium (vol. 1, p. 115).

Benzophenone. Carry out the test as described under "Thin-layer chromatography (vol. 1, p. 83), using silica gel R4 as the coating substance and a mixture of 75 volumes of hexane R and 30 volumes of dioxan R as the mobile phase. Apply separately to the plate 5 µl of each of the following 2 solutions. For solution (A) shake a quantity of the powdered tablets equivalent to about 0.1 g of Phenytoin sodium with 5 ml of methanol R, warm on a water-bath with shaking, filter and use the filtrate. For solution (B) use 0.10 mg of benzophenone R per ml of methanol R. After removing the plate from the chromatographic chamber, allow it to dry in air and examine the chromatogram in ultraviolet light (254 nm).

Any spot obtained with solution A, corresponding to benzophenone, is not more intense than that obtained with solution B.

Assay. Weigh and powder 20 tablets. Transfer to a separatory funnel a quantity of the powdered tablets equivalent to about 0.3 g of Phenytoin sodium, add 25 ml of water and shake. Add 50 ml of ether R, shake and add 10 drops of bromophenol blue/ethanol TS. Titrate with hydrochloric acid (0.1 mol/l) VS, shaking vigorously, until the colour of the aqueous layer turns to bluish-grey. Transfer the aqueous layer to a stoppered conical flask. Wash the ether layer with 5 ml of water and combine the washing with the aqueous layer in the conical flask. Add 20 ml of ether R and continue the titration with hydrochloric acid (0.1 mol/l) VS, shaking vigorously, until the colour of the aqueous layer turns to pale green.

Each ml of hydrochloric acid (0.1 mol/l) VS is equivalent to 27.43 mg of $C_{15}H_{11}N_2NaO_2$.

Dissolution test. (See introduction).

PRAZIQUANTELI COMPRESSI

Praziquantel tablets

Category. Anthelmintic drug.

Additional information. Strength in the current WHO Model list of essential drugs: 150 mg, 600 mg.

REQUIREMENTS

Complies with the monograph for "Tablets" (vol. 4, p. 26).

Praziquantel tablets contain not less than **90.0%** and not more than **110.0%** of the amount of $C_{19}H_{24}N_2O_2$ stated on the label.

Identity tests

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

To a quantity of the powdered tablets equivalent to about 0.1 g of Praziquantel add 10 ml of chloroform R, shake and filter. Evaporate the filtrate to dryness and dry the residue at 50 °C under reduced pressure (not exceeding 0.6 kPa or about 5 mm of mercury). Use the residue for tests A and D.

A. Carry out the examination with the residue as described under "Spectrophotometry in the infrared region" (vol. 1, p. 40). The infrared absorption spectrum is concordant with the spectrum obtained from praziquantel RS or with the *reference spectrum* of praziquantel.

B. See the test described below under "Related substances". The principal spot obtained with solution A corresponds in position, appearance, and intensity with that obtained with solution B.

C. The absorption spectrum of the solution obtained in the "Assay", when observed between 230 nm and 350 nm, exhibits two maxima at about 264 nm and 272 nm.

D. Melting temperature of the residue, about 138 °C.

Related substances. Carry out the test as described under "Thin-layer chromatography (vol. 1, p. 83), using silica gel R5 as the coating substance and a mixture of 85 volumes of toluene R and 15 volumes of methanol R as the mobile phase. Apply separately to the plate, in a current of nitrogen R, 10 µl of each of the following 2 solutions. For solution (A) shake a quantity of the powdered tablets equivalent to about 0.25 g of Praziquantel with 5 ml of chloroform R, filter and use the filtrate. For solution (B) use 0.05 g of praziquantel RS per ml of chloroform R. Further apply 2 µl of each of the following 2 solutions in chloroform R containing (C) 0.5 mg of praziquantel RS per ml and (D) 1.0 mg of praziquantel RS per ml. Allow the mobile phase to ascend 7 cm. After removing the plate from the chromatographic chamber, allow it to dry in a current of warm air, place the plate in a chamber with iodine vapours and allow to stand for 20 minutes. Examine the chromatogram immediately in daylight.

Any spot obtained with solution A, other than the principal spot, is not more intense than that obtained with solution C, except one spot above the main spot which is not more intense than that obtained with solution D.

Assay. Weigh and powder 20 tablets. To a quantity of the powder equivalent to about 25 mg of Praziquantel add 50 ml of ethanol (~750 g/l) TS, shake and dilute to volume with the same solvent. Filter and discard the first 5 ml of the filtrate. Measure the absorbance of a 1-cm layer at the maximum at about 264 nm, against a solvent cell containing ethanol (~750 g/l) TS. Calculate the content of $C_{19}H_{24}N_2O_2$ by comparison with a solution containing 0.50 mg of Praziquantel RS per ml of ethanol (~750 g/l) TS.

PREDNISOLONI COMPRESSI

Prednisolone tablets

Category. Adrenal hormone.

Additional information. Strength in the current WHO Model list of essential drugs: 1 mg, 5 mg.

REQUIREMENTS

Complies with the monograph for "Tablets" (vol. 4, p. 26).

Prednisolone tablets contain not less than 90.0% and not more than 110.0% of the amount of $C_{21}H_{28}O_5$ stated on the label.

Identity tests

- *Either test A alone or tests B and C may be applied.*

To a quantity of the powdered tablets equivalent to about 0.05g of Prednisolone add 10 ml of acetone R, shake and filter. Evaporate the filtrate to dryness and use the residue for the "Identity tests" and the "Related substances".

- A. Carry out the examination with the residue as described under "Spectrophotometry in the infrared region" (vol. 1, p. 40). The infrared absorption spectrum is concordant with the spectrum obtained from prednisolone RS or with the *reference spectrum* of prednisolone.
- B. Carry out the test as described under "Thin-layer chromatography (vol. 1, p. 83), using kieselguhr R1 as the coating substance and a mixture of 1 volume of formamide R and 9 volumes of acetone R to impregnate the plate, dipping it about 5 mm into the liquid. After the solvent has reached a height of at least 16 cm, remove the plate from the chromatographic chamber and allow it to stand at room temperature until the solvent has completely evaporated. Use the impregnated plate within 2 hours, carrying out the chromatography in the

same direction as the impregnation. Use chloroform R as the mobile phase. Apply separately to the plate 2 μ l of each of 2 solutions in a mixture of 9 volumes of chloroform R and 1 volume of methanol R containing (A) 2.5 mg of the residue per ml, and (B) 2.5 mg of prednisolone RS per ml. Develop the plate for a distance of 15 cm. After removing the plate from the chromatographic chamber, allow it to dry in air until the solvents have evaporated, heat at 120 °C for 15 minutes, and spray the hot plate with sulfuric acid/ethanol TS. Heat at 120 °C for a further 10 minutes, allow to cool, and examine the chromatogram in daylight and in ultraviolet light (365 nm).

The principal spot obtained with solution A corresponds in position, appearance, and intensity with that obtained with solution B.

C. To 5 mg of the residue add 1.0 ml of ethanol (~750 g/l) TS and shake. Then add 1.0 ml of potassium-cupric tartrate TS and heat to boiling; an orange precipitate is produced slowly.

Related substances. Carry out the test as described under "Thin-layer chromatography (vol. 1, p. 83), using silica gel R2 as the coating substance and a mixture of 77 volumes of dichloromethane R, 15 volumes of ether R, 8 volumes of methanol R and 1.2 volumes of water as the mobile phase. Apply separately to the plate 1 μ l of each of 2 solutions in a mixture of 9 volumes of chloroform R and 1 volume of methanol R containing (A) 15 mg of the residue per ml and (B) 0.30 mg of the residue per ml. After removing the plate from the chromatographic chamber, allow it to dry in air until the solvents have evaporated and heat at 105 °C for 10 minutes; cool, 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. Weigh and powder 20 tablets. To a quantity of the powdered tablets equivalent to about 20 mg of Prednisolone, add 15 ml of water, shake with four quantities, each of 25 ml, of chloroform R and filter the chloroform layer through cotton wool previously washed with chloroform R. Add sufficient chloroform R to the filtrate to produce 250 ml and dilute 25 ml to 100 ml with the same solvent. Transfer 10 ml of the resulting solution into a glass-stoppered, 50-ml conical flask, carefully evaporate to dryness and dissolve the residue in 20 ml of dehydrated ethanol R. Transfer 20 ml of dehydrated ethanol R to a similar flask to serve as the blank. To each of the flasks add 2.0 ml of blue tetrazolium/ethanol TS, and mix. Then add to each flask 2.0 ml of tetramethylammonium hydroxide/ethanol TS, mix, and allow to stand in the dark for 90 minutes. Measure the absorbance of a 1-cm layer at the maximum at about 525 nm against a solvent cell containing the blank.

Calculate the content of $C_{21}H_{28}O_5$ in the tablets being tested by comparison with prednisolone RS, similarly and concurrently examined.

Uniformity of content.

For tablets containing 1 mg of Prednisolone. Individually transfer 10 powdered tablets to 10 separate 100-ml volumetric flasks add 50 ml of ethanol (~750 g/l) TS, shake and dilute to volume with the same solvent.

For tablets containing 5 mg of Prednisolone. Individually transfer 10 powdered tablets to 10 separate 100-ml volumetric flasks add 50 ml of ethanol (~750 g/l) TS, shake and dilute to volume with the same solvent. Dilute 2.0 ml to 10 ml with ethanol (~750 g/l) TS. Measure the absorbance of a 1-cm layer of the solutions at the maximum at about 242 nm.

Calculate the content in mg of $C_{21}H_{28}O_5$ in each tablet by comparison with prednisolone RS. The tablets comply with the test for "Uniformity of content for single dose preparations" (vol. 4, p. 46).

PYRANTELI EMBONATIS COMPRESSI

Pyrantel embonate tablets

Category. Anthelmintic drug.

Additional information. Strength in the current WHO Model list of essential drugs: 250 mg of pyrantel.

REQUIREMENTS

Complies with the monograph for "Tablets" (vol. 4, p. 26).

Pyrantel embonate tablets contain not less than **90.0%** and not more than **110.0%** of the amount of $C_{11}H_{14}N_2S, C_{23}H_{16}O_6$ stated on the label.

Identity tests

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

To a quantity of the powdered tablets equivalent to about 0.05 g of Pyrantel embonate add a mixture of 10 ml of chloroform R, 10 ml of methanol R and about 1 ml of ammonia (~260 g/l) TS, shake and filter. Evaporate the filtrate to dryness on a water-bath, dissolve in a small volume of methanol R and allow to recrystallize. Separate the crystals and dry at 80 °C for 2 hours and use the dried crystals for the "Identity tests" and the "Related substances".

- A. Carry out the examination with the dried crystals as described under "Spectrophotometry in the infrared region" (vol. 1, p. 40). The infrared absorption spectrum is concordant with the spectrum obtained from pyrantel embonate RS or with the *reference spectrum* of pyrantel embonate.
- B. See the test described below under "Related substances". The principal spot obtained with solution A corresponds in position, appearance, and intensity with that obtained with solution B.
- C. Dissolve 5 mg of the dried crystals in 1.0 ml of hydrochloric acid (~70 g/l) TS and add 1.0 ml of formaldehyde/sulfuric acid TS; a violet-red colour is produced.
- D. Dissolve about 2 mg of the dried crystals in 2 ml of sulfuric acid (~1760 g/l) TS; a yellow colour is produced which changes to orange and finally to red.

Related substances. Carry out the test as described under "Thin-layer chromatography (vol. 1, p. 83), using silica gel R2 as the coating substance and a mixture of 20 volumes of ethyl acetate R, 5 volumes of methanol R and 1.5 volumes of diethylamine R as the mobile phase. Apply separately to the plate 100 µl of each of 3 solutions in a mixture of 5 volumes of chloroform R, 5 volumes of methanol R and 0.5 volume of ammonia (~260 g/l) TS containing (A) 20 mg of the dried crystals per ml, (B) 20 mg pyrantel embonate RS per ml, and (C) of 0.20 mg of the dried crystals per ml. After removing the plate from the chromatographic chamber, allow it to dry in a current of air for 10 minutes, 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 C.

Assay.

Note. The operations described below must be carried out in subdued light and without any prolonged interruptions, preferably using low-actinic glassware.

Weigh and powder 20 tablets. To a quantity of the powdered tablets equivalent to about 0.1 g, add 10 ml of dioxan R and 10 ml of ammonia (100 g/l) TS and shake for 10 minutes. Dilute to 100 ml with perchloric acid (~140 g/l) TS, filter, discard the first 10 ml of the filtrate, and transfer 5 ml of the subsequent filtrate to a 50-ml volumetric flask. Dilute to volume with perchloric acid (~140 g/l) TS and mix. Transfer 25 ml to a 250-ml separating funnel, add 100 ml of chloroform R, and shake well. Drain off the chloroform layer into a second separating funnel. Repeat the extraction of the aqueous phase with a second 100-ml portion of chloroform R, and combine the chloroform extracts into the same separating funnel. Add 40 ml of hydrochloric acid (0.05 mol/l) VS to the combined chloroform extracts and shake well. Drain off the chloroform phase into a third separating funnel and extract with a further 40-ml portion of hydrochloric acid (0.05 mol/l) VS, discarding the chloroform phase. Combine the aqueous phases in a 100-ml volumetric flask, rinse the separating funnel,

draining into the volumetric flask, and dilute to volume with hydrochloric acid (0.05 mol/l) VS. Measure the absorbance of a 1-cm layer at the maximum at about 311 nm against a solvent cell containing hydrochloric acid (0.05 mol/l) VS.

Calculate the content of $C_{11}H_{14}N_2S$, $C_{23}H_{16}O_6$ in the tablets being tested by comparison with pyrantel embonate RS, similarly and concurrently examined.

3. Reagents

Aluminium oxide R. Al_2O_3 . A suitable grade for use in thin-layer chromatography.

Anisaldehyde R. $C_8H_8O_2$.

Description. A colourless to pale yellow, oily liquid; odour, aromatic.

Mass density. ρ_{20} = about 1.125 kg/l.

Boiling temperature. About 248 °C.

Benzophenone R. $C_{13}H_{10}O$.

Melting point. About 49 °C.

A commercially available reagent of suitable grade.

Codeine phosphate RS. International Chemical Reference Substance.

Doxycycline hyclate RS. International Chemical Reference Substance.

6-Epidoxycycline hydrochloride RS. International Chemical Reference Substance.

Metacycline RS. International Chemical Reference Substance.

***p*-Methoxybenzaldehyde R.** $C_8H_8O_2$.

Description. A yellow liquid.

Refractive index ($n_{20}^{20/D}$). 1.5724–1.5744.

Morphine sulfate RS. International Chemical Reference substance.

Pethidine hydrochloride RS. International Chemical Reference Substance.

Phenobarbital RS. International Chemical Reference Substance.

Phosphate buffer, pH 7.2, TS.

Procedure. Dissolve 6.80 g of potassium dihydrogen phosphate R and 1.4 g of sodium hydroxide R in sufficient water to produce 1000 ml.

Sodium nitrate R. NaNO_3 .

A commercially available reagent of suitable grade.

Tetrabutylammonium hydrogen sulfate. $\text{C}_{16}\text{H}_{37}\text{NO}_4\text{S}$.

Description. Colourless crystals or a crystalline powder.

Solubility. Freely soluble in water and methanol R.

A commercially available reagent of suitable grade.

Trinitrophenol/ethanol TS.

Procedure. Dissolve 33 g of trinitrophenol R in sufficient ethanol (~750 g/l) TS to produce 1000 ml.

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