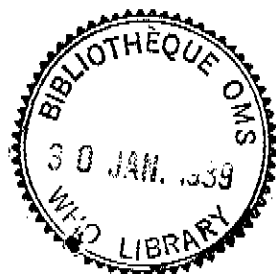




THE INTERNATIONAL PHARMACOPOEIA
THIRD EDITION
PHARMACOPOEA INTERNATIONALIS
EDITIO TERTIA



PHARMACEUTICAL AIDS
(Draft)
Part 3

WORLD HEALTH ORGANIZATION
GENEVA
1989

Comments on this draft document are kindly invited and should be forwarded to WHO, Pharmaceuticals, Attention: Dr A. Mechkovski, 1211 Geneva 27, Switzerland, no later than 3 months after the date of distribution of the document.

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1. Preface

Further to document WHO/PHARM/88.538 additional draft monographs for pharmaceutical aids¹ for the third edition of the International Pharmacopoeia are presented for consultation. The present issue comprises 20 draft monographs of a wide variety of categories, e.g. solvents, acidifying agents, tablet and capsule binders, diluents, suspending agents, viscosity-increasing agents, stabilizers, nonionic surfactants, etc. Many of the pharmaceutical aids are listed under more than one category.

The articles are selected from a previously established list of widely used pharmaceutical aids.

Three monographs in this document are in need of a test for the Hydroxyl value which is not provided in volume 1 of the International Pharmacopoeia. A first draft of this test method is included under item 5.

¹WHO/PHARM/88.538 - Draft monographs for pharmaceutical aids.

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We would be grateful if, in formulating your comments you would refer to the "Guidance for those preparing and commenting on monographs for inclusion in the International Pharmacopoeia"² and the "Guidance for those preparing or commenting on monographs for preparations to be included in the International Pharmacopoeia"³.

2. Monographs

Acidum hydrochloricum
Acidum hydrochloricum dilutum
Adeps solidus
Amyla
Aqua pro injectione
Aqua purificata
Aqua sterilisata pro injectione
Carbomerum
Carmellosum natricum
Cera cetyla
Cetomacrogolum 1000
Dinatrii edetas
Hydroxyethylcellulosum
Hypromellosum
Kaolinum
Magnesii stearas
Polysorbata 20, 60, 80
Polyvidonum
Saccharinum natricum
Talcum

ACIDUM HYDROCHLORICUM

Hydrochloric Acid

Description. A clear, colourless, fuming liquid; odour, pungent.

Miscibility. Miscible with water.

Category. Acidifying agent.

Storage. Hydrochloric Acid should be kept in a tightly closed container.

Additional information. The fumes and odour of the acid disappear when it is diluted with 2 volumes of water. Hydrochloric Acid is strongly acid to litmus TS even when highly diluted.

²WHO Technical Report Series, No. 704, 1984, Annex 5 (Twenty-ninth report of the WHO Expert Committee on Specifications for Pharmaceutical Preparations).

³WHO/PHARM/88.534.

REQUIREMENTS

General requirement. Hydrochloric Acid contains not less than 35.0 % m/m and not more than 38.0 % m/m of HCl.

Identity tests

- A. It is strongly acid.
- B. Use 0.1 ml; it yields the reactions as described under "General identification tests" as characteristic of chlorides (vol.1, p.113).
- C. Allow a glass stick wetted with ammonia (~100 g/l)TS to come near the surface of Hydrochloric Acid; white smoke is evolved.

Mass density. ρ_{20} = about 1.18.

Heavy metals. For the preparation of the test solution evaporate 4 g to dryness on a water-bath, add 2.0 ml of acetic acid (~60 g/l) PbTS, dilute to 40 ml and mix; determine the heavy metals content as described under "Limit test for heavy metals", according to method A (vol.1, p.119); not more than 5 $\mu\text{g/g}$.

Arsenic. Not more than 2 $\mu\text{g/g}$.

For the following 3 tests mix 1 volume of Hydrochloric Acid with 2 volumes of water:

Bromides and iodides. To 10 ml add 1.0 ml of chloroform R and add cautiously, a drop at a time with constant stirring, chlorine TS which has been diluted with an equal volume of water; the chloroform remains free from even a transient yellow, orange or violet colour.

Free bromine and chlorine. To 10 ml add 1.0 ml of potassium iodide (80 g/l)TS and 1.0 ml of chloroform R, and shake the mixture; the chloroform remains free from any violet coloration for at least 1 minute.

Sulfites. Mix 3 ml with 5 ml of water, add 5 drops of barium chloride (50 g/l)TS and 2 drops of iodine (0.05 mol/l)VS; no turbidity is produced and the colour of the iodine is not completely discharged.

Sulfates. To 20 ml of Hydrochloric Acid add 40 mg of sodium hydrogen carbonate R and evaporate to dryness on a water-bath; dissolve the residue in 20 ml of water and proceed as described under "Limit test for sulfates" (vol.1, p.116); the sulfate content is not more than 20 $\mu\text{g/g}$.

Residue on ignition. Place about 10 g, accurately weighed, in a porcelain dish and evaporate to dryness on a water-bath. Ignite the residue to constant weight; not more than 0.1 mg/g of residue.

Assay. Add about 1.5 ml to a tared glass-stoppered flask containing about 20 ml of water, and reweigh; add about 25 ml of water and titrate with sodium hydroxide (1 mol/l)VS, using methyl red/ethanol TS as indicator. Each ml of sodium hydroxide (1 mol/l)VS is equivalent to 36.46 mg of HCl.

ACIDUM HYDROCHLORICUM DILUTUM

Dilute Hydrochloric Acid

Description. A colourless liquid, odourless.

Category. Acidifying agent.

Storage. Dilute Hydrochloric Acid should be kept in a tightly closed container.

Additional information. Dilute Hydrochloric Acid is strongly acid to litmus TS.

REQUIREMENTS

General requirement. Dilute Hydrochloric Acid contains not less than 9.5 % m/m and not more than 10.5 % m/m of HCl.

Identity tests

- A. It is strongly acid.
- B. Use 0.5 ml; it yields the reactions as described under "General identification tests" as characteristic of chlorides (vol. 1, p.113).

Mass density. $\rho_{20} = 1.043 - 1.049$.

Heavy metals. For the preparation of the test solution evaporate 4 g to dryness on a water-bath, add 2.0 ml of acetic acid (~60 g/l) PbTS, dilute to 40 ml and mix; determine the heavy metals content as described under "Limit test for heavy metals", according to Method A (vol. 1, p.119); not more than 5 µg/g.

Arsenic. Not more than 0.5 µg/g.

Bromides and iodides. To 10 ml add 1.0 ml of chloroform R and add cautiously, a drop at a time with constant stirring, chlorine TS which has been diluted with an equal volume of water; the chloroform remains free from even a transient yellow, orange or violet colour.

Free bromine and chlorine. To 10 ml add 1.0 ml of potassium iodide (80 g/l) TS and 1.0 ml of chloroform R, and shake the mixture; the chloroform remains free from any violet coloration for at least 1 minute.

Sulfites. Mix 3 ml with 5 ml of water, add 5 drops of barium chloride (50 g/l) TS and 2 drops of iodine (0.05 mol/l) VS; no turbidity is produced and the colour of the iodine is not completely discharged.

Sulfates. To 90 ml add 40 mg of sodium hydrogen carbonate R and evaporate to dryness on a water-bath; dissolve the residue in 20 ml of water and proceed as described under "Limit test for sulfates" (vol. 1, p.116); the sulfate content is not more than 5 µg/g.

Residue on ignition. Place about 10 g, accurately weighed, in a porcelain dish and evaporate to dryness on a waterbath. Ignite the residue to constant weight; not more than 0.1 mg/g of residue.

Assay. Mix 2 ml, accurately weighed, with 20 ml of water and titrate with sodium hydroxide (1 mol/l) VS, using methyl red/ethanol TS as indicator. Each ml of sodium hydroxide (1 mol/l) VS is equivalent to 36.46 mg of HCl.

ADEPS SOLIDUS

Hard Fat

Composition. Hard Fat is a mixture of mono-, di- and triglyceride esters of higher saturated fatty acids ($C_{10}H_{20}O_2$ to $C_{18}H_{36}O_2$).

Description. A white, brittle mass; almost odourless; unctuous.

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

Category. Suppository base.

Storage. Hard Fat should be kept in a well-closed container, protected from light and stored at a temperature not exceeding 5 °C below the melting range.

Additional information. On warming, hard fat melts to a colourless to slightly yellow liquid. On shaking the molten material with an equal quantity of hot water, it forms a white emulsion.

Note: For certain applications, it may be necessary to comply to different specifications that are more restricted.

REQUIREMENTS

Melting range (vol. 1, p. 23). Cool the charged tube at a temperature below 10 °C for 24 hours; 3 - 40 °C.

Acid value (vol. 1, p. 140). Not more than 1.0.

Hydroxyl value (see item 5). Use method B; not more than 50.

Iodine value (vol. 1, p. 137). Not more than 7.

Peroxide value (vol. 1, p. 138). Not more than 6.

Saponification value (vol. 1, p. 139). Use 2.0 g; 220 - 250.

Unsaponifiable matter (vol. 1, p. 139). Use 5.0 g; not more than 1.0 %.

Ash (vol. 1, p. 161). Not more than 0.5 mg/g.

AMYLE

Starches

Composition. Starches consist of polysaccharide granules obtained from the grains of corn (Zea mays L.), of rice (Oryza sativa L.), of wheat (Triticum aestivum L.), or from the tubers of the potato (Solanum tuberosum L.).

Description. Fine, white to slightly yellowish powder or ovoid granules whose size and shape are characteristic for each botanical variety; odourless.

Solubility. Practically insoluble in cold water and ethanol (~750 g/l)TS.

Category. Tablet and capsule binder, diluent, disintegrant.

Storage. Starches should be kept in tightly closed containers.

Labelling. The designation on the container of starches should state the botanical source.

Additional information. Types of starches should not be interchanged since the properties are characteristic for each one obtained from different botanical sources and therefore, their performance may not be identical. Attention should be paid to the microbiological purity since starches are of natural origin.

REQUIREMENTS

Identity tests

- A. To 1 g add 50 ml of water, heat to boiling for 1 minute and cool; a thin cloudy mucilage is obtained from all starches other than potato starch, which gives a thicker and more translucent mucilage (keep the mucilages for test B.)
- B. To about 1 ml of the mucilage obtained in test A add 0.05 ml of iodine (0.005 mol/l)VS and mix; a dark blue colour is obtained which disappears on heating and reappears on cooling.

Microscopic examination

Corn starch - Angular polyhedral or rounded granules, up to 35 μm in diameter; central hilum consisting of a distinct cavity or several rayed central clefts.

Rice starch - Polyhedral granules, about 2 - 10 μm in size, either isolated or aggregated in ovoid masses; central hilum poorly visible.

Wheat starch - Two distinct types of granules, either simple lenticular, 20 - 50 μm in diameter, or small spherical, 5 - 10 μm in diameter; hilum and striations poorly visible.

Potato starch - simple granules, either irregular, ovoid or spherical granules, up to 100 μm in size; hilum near the narrower end; striations well marked and concentric.

Sulfated ash

Corn starch - not more than 6 mg/g.
Rice starch - not more than 10 mg/g.
Wheat starch - not more than 6 mg/g.
Potato starch - not more than 6 mg/g.

Loss on drying. Dry to constant weight at 100 °C;

Corn starch - not more than 150 mg/g.
Rice starch - not more than 150 mg/g.
Wheat starch - not more than 150 mg/g.
Potato starch - not more than 200 mg/g.

Acidity. To 10 g add 100 ml of ethanol (~600 g/l)TS previously neutralized to phenolphthalein/ethanol TS, shake for 1 hour, filter and titrate 50 ml of the filtrate with sodium hydroxide (0.1 mol/l)VS; not more than 2.0 ml is required to change the colour of the solution.

Foreign matter. Using a microscope, not more than traces of cell debris are present, and it does not contain granules of any other origin than the type of starch stated on the label.

Sulfur dioxide. Mix 20 g with 200 ml of water until a smooth suspension is obtained and filter. To 100 ml of the clear filter add 3 ml of starch TS and titrate with iodine (0.005 mol/l)VS until a permanent blue colour is obtained; not more than 2.7 ml is required (0.08 mg/g).

AQUA PRO INJECTIONE
Water for Injections^{*}

Molecular formula. H₂O

Relative molecular mass. 18.02

Chemical name. Hydrogen oxide; CAS Reg. No. 7732-18-5.

^{*} See page 37.

Description. Water for Injections is a clear and colourless liquid; odourless. It is obtained from potable or Purified Water by distillation in an apparatus of which the parts in contact with the liquid are of neutral glass, quartz or suitable metal and which is fitted with an effective device to prevent entrainment of droplets. The first portion of the distillate obtained when the apparatus begins to function is discarded. The distillate is collected and stored in conditions designed to prevent growth of microorganisms and to avoid any other contamination.

Category. Solvent for parenteral preparations.

Labelling. Water for Injections is non-sterile.

Storage. Water for Injections should be kept in a well-closed container.

Additional information. Water for Injections is subsequently used for Sterile Water for Injections.

Caution: Water for Injections is non-sterile.

REQUIREMENTS

Complies with the general requirements for
"Parenteral Preparations" WHO/PHARM/88.533 Rev.1

Heavy metals. Take 40 ml of the test liquid the pH of which has been adjusted with acetic acid (~60 g/l)PbTS as described under "Limit test for heavy metals", procedure 1 (vol. 1, p. 118); determine the heavy metals content according to Method A allowing to stand for 10 minutes; the colour is not darker than 40 ml of the same liquid the pH of which has been similarly adjusted.

Ammonia. Transfer 50 ml to a comparison tube and add 2 ml of alkaline potassio-mercuric iodide TS; when viewing down the vertical axis of the tube in diffused light against a white background the colour is not more intense than that of 50 ml of ammonia-free water R with the addition of 2 ml of dilute ammonium chloride TS (Nessler's).

Calcium and magnesium. To 100 ml add 2 ml of ammonium chloride buffer, pH 10.0, TS, 50 mg of mordant black 11 R and 0.5 ml of disodium edetate (0.01 mol/l) VS; a pure blue colour is produced.

Carbon dioxide. To 25 ml add 25 ml of calcium hydroxide TS; the mixture remains clear.

Chlorides. To 10 ml add 1 ml of silver nitrate (40 g/l)TS and allow to stand for 5 minutes; the liquid remains clear and colourless.

Nitrates. Carefully superimpose 5 ml on 5 ml of diphenylamine/sulfuric acid TS, ensuring that the liquids do not mix; no blue colour is produced at the interface of the two liquids.

Sulfates. To 10 ml add 1 ml of barium chloride (50 g/l)TS and allow to stand for 5 minutes; the liquid remains clear and colourless.

Oxidizable matter. To 100 ml add 10 ml of sulfuric acid (~100 g/l)TS, 0.2 ml of potassium permanganate (0.02 mol/l)VS and boil for 3 minutes; the colour is not completely destroyed.

Non-volatile residue. Evaporate 500 ml on a water-bath to dryness and dry the residue for 1 hour at 105 °C; not more than 5 mg (0.01 mg/ml).

Acidity or alkalinity. To 10 ml add 2 drops of methyl red/ ethanol TS; no red colour is produced. To a further 10 ml portion add 5 drops of bromothymol blue/ethanol TS; no blue colour is produced.

Pyrogens. Carry out the test as described under "Test for pyrogens" (vol. 1, p. 155) injecting, per kg of the rabbit's mass, 10 ml of Water for Injections, made sterile and also made isotonic by the addition of pyrogen-free sodium chloride R.

AQUA PURIFICATA
Purified Water

Molecular formula. H₂O

Relative molecular mass. 18.02

Chemical name. Hydrogen oxide; CAS Reg. No. 7732-18-5.

Description. Purified Water is clear, colourless liquid; odourless. It contains no added substance. It is prepared by distillation, ion-exchange treatment, reverse osmosis, or other appropriate process from suitable potable water.

Category. Solvent.

Storage. Purified Water should be kept in a well-closed container.

Labelling. The method of preparation should be indicated on the label.

Additional Information.

Caution:

- Purified Water must not be used for preparations intended for parenteral administration.
- Purified water intended for ophthalmic preparations must be sterilized immediately before use. (Sterilization methods and sterility testing, WHO/PHARM/88.533/Rev.1).

REQUIREMENTS

Heavy metals. Take 40 ml of the test liquid the pH of which has been adjusted with acetic acid (~60 g/l)PbTS as described under "Limit test for heavy metals", procedure 1 (vol. 1, p. 118); determine the heavy metals content according to Method A allowing to stand for 10 minutes; the colour is not darker than 40 ml of the same liquid the pH of which has been similarly adjusted.

Ammonia. Transfer 50 ml to a comparison tube and add 2 ml of alkaline potassio-mercuric iodide TS; when viewing down the vertical axis of the tube in diffused light against a white background the colour is not more intense than that of 50 ml of ammonia-free water R with the addition of 2 ml of dilute ammonium chloride TS (Nessler's).

Calcium and magnesium. To 100 ml add 2 ml of ammonium chloride buffer, pH 10.0, TS, 50 mg of mordant black 11 R and 0.5 ml of disodium edetate (0.01 mol/l) VS; a pure blue colour is produced.

Carbon dioxide. To 25 ml add 25 ml of calcium hydroxide TS; the mixture remains clear.

Chlorides. To 10 ml add 1 ml of silver nitrate (40 g/l)TS and allow to stand for 5 minutes; the liquid remains clear and colourless.

Nitrates. Carefully superimpose 5 ml on 5 ml of diphenylamine/sulfuric acid TS, ensuring that the liquids do not mix; no blue colour is produced at the interface of the two liquids.

Sulfates. To 10 ml add 1 ml of barium chloride (50 g/l)TS and allow to stand for 5 minutes; the liquid remains clear and colourless.

Oxidizable matter. To 100 ml add 10 ml of sulfuric acid (~100 g/l)TS, 0.5 ml of potassium permanganate (10 g/l)TS and boil for 3 minutes; the colour is not completely destroyed.

Non-volatile residue. Evaporate 500 ml on a water-bath to dryness and dry the residue for 1 hour at 105 °C; not more than 5 mg (0.01 mg/ml).

Acidity or alkalinity. To 10 ml add 2 drops of methyl red/ ethanol TS; no red colour is produced. To a further 10 ml portion add 5 drops of bromothymol blue/ethanol TS; no blue colour is produced.

AQUA STERILISATA PRO INJECTIONE
Sterile Water for Injections

Molecular formula. H₂O

Relative molecular mass. 18.02

Chemical name. Hydrogen oxide; CAS Reg. No. 7732-18-5.

Description. Sterile Water for Injections is a pyrogen-free, clear and colourless liquid; odourless. It is sterile (Sterilization methods, WHO/PHARM/88.533/Rev.1) and suitably packaged.

Category. It is a solvent used for dissolving or diluting substances or preparations for parenteral administration.

Storage. Sterile Water for Injection should be kept in a single dose container of not larger than 1-litre size.

Additional Information.

Caution: Sterile Water for Injections is sterile.

REQUIREMENTS

Heavy metals. Take 40 ml of the test liquid the pH of which has been adjusted with acetic acid (~60 g/l)PbTS as described under "Limit test for heavy metals", procedure 1 (vol. 1, p. 118); determine the heavy metals content according to Method A allowing to stand for 10 minutes; the colour is not darker than 40 ml of the same liquid the pH of which has been adjusted similarly.

Ammonia. Transfer 50 ml to a comparison tube and add 2 ml of alkaline potassio-mercuric iodide TS; when viewing down the vertical axis of the tube in diffused light against a white background the colour is not more intense than that of 50 ml of ammonia-free water R with the addition of 2 ml of dilute ammonium chloride TS (Nessler's).

Calcium and magnesium. To 100 ml add 2 ml of ammonium chloride buffer, pH 10.0, TS, 50 mg of mordant black 11 R and 0.5 ml of disodium edetate (0.01 mol/l) VS; a pure blue colour is produced.

Carbon dioxide. To 25 ml add 25 ml of calcium hydroxide TS; the mixture remains clear.

Chlorides. To 10 ml add 1 ml of silver nitrate (40 g/l)TS and allow to stand for 5 minutes; the liquid remains clear and colourless.

Nitrates. Carefully superimpose 5 ml on 5 ml of diphenylamine/sulfuric acid TS, ensuring that the liquids do not mix; no blue colour is produced at the interface of the two liquids.

Sulfates. To 10 ml add 1 ml of barium chloride (50 g/l)TS and allow to stand for 5 minutes; the liquid remains clear and colourless.

Oxidizable matter. To 100 ml add 10 ml of sulfuric acid (~100 g/l)TS, 0.5 ml of potassium permanganate (10 g/l)TS and boil for 3 minutes; the colour is not completely destroyed.

Non-volatile residue. Evaporate 500 ml on a water-bath to dryness and dry the residue for 1 hour at 105 °C; not more than 5 mg (0.01 mg/ml).

Acidity or alkalinity. To 10 ml add 2 drops of methyl red/ ethanol TS; no red colour is produced. To a further 10 ml portion add 5 drops of bromothymol blue/ethanol TS; no blue colour is produced.

Pyrogens. Carry out the test as described under "Test for pyrogens" (vol. 1, p. 155) injecting, per kg of the rabbit's mass, 10 ml of the test liquid and made isotonic by the addition of pyrogen-free sodium chloride R.

Sterility. Complies with the "Tests for Sterility" (WHO/PHARM/88.533/Rev.1).

CARBOMERUM

Carbomer

Composition. Carbomer is a synthetic high molecular weight polymer of acrylic acid copolymerized with polyalkylsucrose.

Description. A white, fluffy powder; odour, slight and characteristic.

Solubility. After neutralization with alkali hydroxides or amines, soluble in water, ethanol (~750 g/l)TS and glycerol R.

Category. Suspending agent.

Storage. Carbomer should be kept in a tightly closed container.

Additional information. Carbomer is very hygroscopic.

REQUIREMENTS

General requirement. Carbomer contains not less than 56.0 % and not more than 68.0 % of carboxylic acid groups (-COOH), calculated with reference to the dried substance.

Identity tests

A. Disperse 0.5 g in 50 ml of water. To 10 ml add a few drops of thymol blue/ethanol TS; the colour of the dispersion is orange. To a further 10 ml add a few drops of cresol red/ethanol TS; the colour is yellow (keep the dispersion for test B).

B. Adjust the pH of the remaining suspension from test A to about 7.5 with sodium hydroxide (1 mol/l)VS; a very viscous gel is produced.

Yield value. Prepare a gel as follows: carefully add 2.5 g to 500 ml of water containing 0.25 g of sodium chloride R in a 1000-ml beaker, while stirring continuously at 990-1010 revolutions per minute, the stirrer shaft set to one side of the beaker and near to the bottom, at an angle of 60 ° from the vertical. Add the substance to be examined slowly at a uniform rate over 45-90 seconds, ensuring that any loose aggregates of powder are broken up. Continue the stirring for 15 minutes, remove the stirrer and allow the beaker containing the dispersion to stand in a water-bath at a temperature of 24.8 - 25.2 °C for 30 minutes. Insert the stirrer to a depth such that air is not drawn into the dispersion and, while stirring at 290-310 revolutions per minute, add 0.2 ml of phenolphthalein/ethanol TS and 1.5 ml of bromothymol blue/ethanol TS. Add rapidly below the surface about 5 ml of sodium hydroxide (~200 g/l)TS, and stir for 2-3 minutes until neutralization is reached indicated by a uniform blue colour. Adjust the pH potentiometrically, using glass and calomel electrodes, to 7.3-7.8, either adding more sodium hydroxide (~200 g/l)TS or preparing a new mucilage using less sodium hydroxide for the neutralization. Return the neutralized mucilage to the water-bath maintained at 25 °C for 1 hour.

The apparatus consists of two clear soda-glass plates, 100 mm x 100 mm x 3 mm. Rub together by hand fine carborundum paste on two opposing faces of the plates to obtain an even matt surface. Using a diamond marker engrave the plates to show centre and corner alignment and four sample location points equidistant from the plate centre and the four corners.

Place the plates in the water-bath at 24.8 - 25.2 °C for equilibration and dry them rapidly before use. Apply 0.1 g of the mucilage to each of the sample location points on the matt surface of one of the plates. Align the second plate and lower it carefully, matt-side downwards, onto the lower plate. Add a suitable weight so that the combined weight of the top plate and applied weight equals 100 g. Allow the assembly to stand for 10 minutes and determine the average zone diameter of each of the four samples using a strip of paper calibrated in mm; mean zone diameter 2.0 - 2.2 cm.

Sulfated ash. Not more than 1.0 mg/g.

Loss on drying. Dry at 80 °C for 1 hour; it loses not more than 20 mg/g.

Assay. Slowly add 0.4 g, accurately weighed and previously dried at 80 °C for 1 hour, to 400 ml of water stirring with a magnetic stirrer until solution is complete. At reduced stirring speed titrate potentiometrically using glass and calomel electrodes with sodium hydroxide (0.2 mol/l)VS. Stir for 1 minute after each addition of sodium hydroxide before recording the pH. Each ml of sodium hydroxide (0.2 mol/l)VS is equivalent to 9.004 mg of carboxylic acid groups (-COOH).

CARMELLOSUM NATRICUM

Carmellose sodium

Composition. Carmellose sodium is the sodium salt of a partially substituted polycarboxymethyl ether of cellulose.

Chemical name. Cellulose carboxymethyl ether sodium salt;
CAS Reg. No. 9004-32-4.

Other name. Carboxymethylcellulose sodium.

Description. A white to faintly yellowish powder or granules; odourless.

Solubility. It is easily dispersed in water giving a colloidal solution; practically insoluble in acetone R, ethanol (~750 g/l)TS, ether R and toluene R.

Category. Suspending agent, tablet binder and disintegrant, viscosity-increasing agent.

Storage. Carmellose sodium should be kept in a tightly closed container.

Labelling. The designation on the container of Carmellose sodium should state its viscosity.

Additional information. Carmellose sodium is hygroscopic after drying. This substance is not necessarily suitable for the manufacture of parenteral preparations. The viscosity of Carmellose sodium should be indicated on the label.

REQUIREMENTS

General requirement. Carmellose sodium contains not less than 6.5 % and not more than 10.8 % of sodium, Na, calculated with reference to the dried substance.

Identity tests

- A. Sprinkle about 1 g of powdered substance on to 90 ml of carbon-dioxide-free water R at 40 - 50 °C, stir vigorously until a colloidal solution is produced, cool and dilute to 100 ml with carbon-dioxide-free water R. (Keep the solution for further tests below). Transfer 0.5 ml of the solution to a test-tube, add 1 ml of water 5 drops of 1-naphthol TS1 and carefully introduce down the side of the tube 2 ml of sulfuric acid (~1760 g/l)TS to form a lower layer; a red-purple colour develops at the interface.
- B. Dissolve the residue obtained in the test for sulfated ash in 1 ml of hydrochloric acid (~420 g/l)TS, evaporate to dryness on a water-bath and dissolve the residue in 20 ml of water. This solution yields reaction B described under "General identification tests" as characteristic of sodium (vol. 1, p. 115).

Chlorides. Use 10 ml of the solution prepared in identity test A and proceed as described under "Limit test for chlorides" (vol. 1, p. 116); the chloride content is not more than 2.5 mg/g.

Clarity and colour of solution. The solution prepared in identity test A is not more intense than opalescence standard TS3 and not more intensely coloured than standard colour solution Yw2 when compared as described under "Colour of liquids" (vol. 1, p. 50).

Sulfated ash. Use 1 g and a mixture of equal volumes of sulfuric acid (~1760 g/l)TS and water. Calculate the result with reference to the dried substance; 0.200 g/g - 0.333 g/g corresponding to a content of Na equivalent to 6.5 - 10.8 %.

Loss on drying. Dry to constant weight at 105 °C; it loses not more than 100 mg/g.

pH value. Use the solution prepared in identity test A; 6.0 - 8.5.

CERA CETYLA
Cetyl esters wax

Composition. Cetyl esters wax is a mixture consisting primarily of esters of saturated fatty alcohols (C₁₄ to C₁₈) and saturated fatty acids (C₁₄ to C₁₈); CAS Reg. No. 977067-67-6.

Other name. Synthetic spermaceti.

Description. White to almost white, somewhat translucent flakes (5 µm to several millimeters in the largest dimension), with a crystalline structure and a pearly luster when caked; odour, faint, mild and aromatic.

Solubility. Practically insoluble in water and ethanol (~750 g/l)TS; soluble in hot ethanol (~750 g/l)TS, chloroform R and ether R; slightly soluble in hexane R.

Category. Stiffening agent.

Storage. Cetyl esters wax should be kept in a well-closed container, protected from heat.

Additional information. Cetyl esters wax was developed to replace spermaceti, which has been banned in certain parts of the world. At 50 °C, it has a mass density of about 0.83 g/ml.

REQUIREMENTS

Melting range (vol. 1, p. 23). 43 - 47 °C.

Acid value (vol. 1, p. 140). Not more than 5.

Iodine value (vol. 1, p. 137). Not more than 1.

Saponification value (vol. 1, p. 139). 109 - 120.

Paraffin. To 1 g add 50 ml of boiling ethanol (~750 g/l)TS; the wax is completely dissolved.

CETOMACROGOLUM 1000

Cetomacrogol 1000

Composition. Cetomacrogol 1000 is a condensation product of linear fatty alcohols with ethylene oxide, prepared under controlled conditions in order to obtain the required ether with the polyethylene glycol of the desired molecular mass.

Chemical name. Polyethylene glycol 1000 monocetyl ether;
CAS Reg. No. 9004-95-9.

Description. A cream-coloured, waxy, unctuous mass, pellets or flakes; when heated it melts to a clear brownish-yellow liquid; odourless or almost odourless.

Solubility. Soluble in water, ethanol (~750 g/l)TS and acetone R; practically insoluble in light petroleum R.

Category. Nonionic surfactant.

Storage. Cetomacrogol 1000 should be kept in a well-closed container, protected from heat.

REQUIREMENTS

Identity tests

- A. Dissolve 0.1 g in 5 ml of water, add 10 ml of hydrochloric acid (~70 g/l)TS, 10 ml of barium chloride (50 g/l)TS and 10 ml of phosphomolybdic acid (80 g/l)TS; a greenish yellow precipitate is produced.
- B. Dissolve 0.1 g in 5 ml of water and add gradually tannic acid (50 g/l)TS; a precipitate is formed which dissolves on further addition of tannic acid solution.

Melting point (vol.1, p. 23). Not lower than 38 °C.

Refractive index. At 60 °C, $n_D^{20} = 1.448 - 1.452$.

Acid value (vol. 1, p. 140). Not more than 0.5.

Alkalinity. Dissolve 2 g in 20 ml of carbon-dioxide-free water R, add 1 drop of phenolphthalein/ethanol TS and titrate with hydrochloric acid (0.1 mol/l)VS; not more than 0.5 ml is required to obtain a pink colour.

Hydroxyl value (see item 5). Use 10 g, method A; 40.0 - 52.5.

Saponification value (vol. 1, p. 139). Use 10 g; not more than 1.0.

Water. Determine as described under "Determination of water by the Karl Fischer method", Method A (vol. 1, p. 135), using about 2.5 g of the substance; the water content is not more than 10 mg/g.

DINATRII EDETAS
Disodium edetate

Molecular formula. $C_{10}H_{14}N_2Na_2O_8 \cdot 2H_2O$

Relative molecular mass. 372.2

Graphic formula.

Chemical name. N,N' -1,2-Ethanediybis(N -(carboxymethyl)-glycine disodium salt dihydrate; disodium (ethylenedinitrilo)tetraacetate dihydrate;
CAS Reg. No. 6381-92-6.

Other name. Edetate disodium.

Description. A white, crystalline powder; odourless.

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

Category. Stabilizer, chelating agent.

Storage. Disodium edetate should be kept in a well-closed container.

Additional information. Solutions of edetate sodium should not come into contact with metal.

REQUIREMENTS

General requirement. Disodium edetate contains not less than 98.5 % and not more than 101.0 % of $C_{10}H_{14}N_2Na_2O_8 \cdot 2H_2O$.

Identity tests

- Either tests A and D or tests B, C and D may be applied.
- A. Carry out the examination as described under "Spectrophotometry in the infrared region" (vol. 1, p. 40). The infrared absorption spectrum is concordant with the spectrum obtained from disodium edetate RS or with the reference spectrum of disodium edetate.
- B. To 3 drops of ferric chloride (25 g/l)TS add 3 drops of ammonium thiocyanate (75 g/l)TS; to the deep red solution add 0.05 g of the test substance; the deep red colour is discharged leaving a yellowish solution (keep the solution for test D).
- C. Dissolve 2.0 g in 25 ml of water, add 2.0 ml of lead nitrate (100 g/l)TS, shake and add 6 ml of potassium iodide (80 g/l)TS; no yellow precipitate is produced.
- D. To the solution from test B add ammonia (~100 g/l)TS, drop by drop, until an alkaline reaction is obtained with pH-indicator paper R. Add 5 ml of ammonium oxalate (25 g/l)TS; no precipitate is produced (distinction from sodium calcium edetate).

Heavy metals. Use 1.0 g for the preparation of the test solution as described under "Limit test for heavy metals", Procedure 3 (vol. 1, p. 118); determine the heavy metals content according to Method A (vol. 1, p. 119); not more than 20 µg/g.

pH Value. pH of a 0.05 g/ml solution, 4.0 - 5.5.

Assay. Dissolve 0.5 g, accurately weighed, in sufficient water to produce 300 ml. Add 2 g of methenamine R and 2 ml of hydrochloric acid (~70 g/l)TS. Titrate with lead nitrate (0.1 mol/l)VS to which 50 mg of xylenol orange indicator mixture R has been added. Each ml of lead nitrate (0.1 mol/l)VS is equivalent to 37.22 mg of $C_{10}H_{14}N_2Na_2O_8 \cdot 2H_2O$.

HYDROXYETHYLCELLULOSUM

Hydroxyethylcellulose

Composition. Hydroxyethylcellulose is a partially substituted poly(hydroxyethyl) ether of cellulose; CAS Reg. No. 9004-62-0.

Description. A white or yellowish white powder or granules; odourless or almost odourless.

Solubility. Soluble in hot and cold water forming a colloidal solution; practically insoluble in acetone R, ethanol (~750 g/l)TS, ether R and toluene R.

Category. Stabilizer, suspending agent.

Storage. Hydroxyethylcellulose should be kept in a well-closed container.

Labelling. The designation on the container of hydroxyethylcellulose should state its viscosity.

Additional information. Hydroxyethylcellulose may contain suitable anti-caking agents. After drying, it is hygroscopic. The viscosity of Hydroxyethylcellulose should be indicated on the label.

REQUIREMENTS

Identity tests

- A. Disperse 1.0 g of dried test substance in 50 ml of carbon-dioxide-free water R. After 10 minutes, dilute to 100 ml with carbon-dioxide-free water R and stir until dissolution is complete (keep this solution for test B and the pH value). Heat 10 ml on a water-bath while stirring; at a temperature above 50 °C no cloudiness or precipitate is observed.
- B. Place 1 ml of the above solution onto a glass plate and allow to evaporate; a thin film is formed.
- C. Dissolve 5 mg in 1.0 ml of water, add 1.0 ml of phenol (50 g/l)TS, 5 ml of sulfuric acid (~1760 g/l)TS, shake carefully and allow to cool; a red colour is developed.

Heavy metals. Use 1.0 g for the preparation of the test solution as described under "Limit test for heavy metals", Procedure 3 (vol. 1, p. 118); determine the heavy metals content according to Method A (vol. 1, p. 119); not more than 20 µg/g.

Sulfated ash. Not more than 50 mg/g.

Loss on drying. Dry to constant weight at 105 °C; it loses not more than 100 mg/g.

pH value. pH of the solution prepared in identity test A, 5.5 - 8.5.

HYPROMELLOSUM

Hypromellose

Composition. Hypromellose is a propylene glycol ether of methylcellulose; CAS Reg. No. 9004-65-3.

Description. A white or creamy white, fibrous or granular powder; odourless or almost odourless.

Solubility. Soluble in cold water, forming a clear or viscous, colloidal solution; practically insoluble in ethanol (~750 g/l)TS, ether R and chloroform R; soluble in mixtures of methanol R and dichloromethane R.

Category. Suspending agent, tablet binder, viscosity-increasing agent.

Storage. Hypromellose should be kept in a well-closed container.

Labelling. The designation on the container of Hypromellose should state its viscosity.

Additional information. The viscosity of Hypromellose should be indicated on the label.

REQUIREMENTS

Identity tests

- A. Disperse 1.0 g of test substance in 100 ml of water, allow the beaker to stand until the substance becomes transparent and mucilaginous (about 5 hours), swirl the beaker and stir until dissolution is complete (keep this solution for test B and the pH value). To two 10-ml aliquots of the solution add an equal volume either of sodium hydroxide (1 mol/l)VS or hydrochloric acid (1 mol/l)VS; the mixture remains stable.
- B. Place 1 ml of the above solution onto a glass plate and allow to evaporate; a thin film is formed.
- C. Add 1 g to 100 ml of boiling water and stir the mixture; a slurry is formed, but the powdered material does not dissolve. Cool the slurry to 20° C and stir; the resulting liquid is a clear or opalescent mucilaginous colloidal mixture.

Heavy metals. Use 1.0 g for the preparation of the test solution as described under "Limit test for heavy metals", Procedure 3, (vol. 1, p. 118) adding 1 ml of hydroxylamine hydrochloride (200 g/l)TS to the solution of the residue; determine the heavy metals content according to Method A (vol. 1, p. 119); not more than 10 µg/g.

Sulfated ash. Not more than 15 mg/g.

Loss on drying. Dry at 105 °C for 2 hours; it loses not more than 50 mg/g.

pH value. pH of the solution prepared in identity test A, 5.0 - 8.0.

KAOLINUM

Kaolin

Composition. Kaolin is a purified, natural hydrated aluminium silicate of variable composition.

Other name. Bolus alba.

Description. A white or greyish white powder, free from gritty particles; onctuous; clay-like odour.

Solubility. Practically insoluble in water and in organic solvents. Insoluble in mineral acids and solutions of alkali hydroxides.

Category. Tablet and capsule diluent, suspending agent.

Storage. Kaolin should be kept in a well-closed container.

Labelling. The designation on the container of kaolin should state if it is intended for internal use.

Additional information. Attention should be paid to the microbiological quality since kaolin is of natural origin.

REQUIREMENTS

Identity tests

- A. Heat 1 g with 10 ml of water and 5 ml of sulfuric acid (~1760 g/l)TS in a porcelain dish, and evaporate the mixture nearly to dryness. Cool, cautiously add 20 ml of water, boil for 2 - 3 minutes and filter; the residue on the filter is grey. Use the filtrate for test B.
- B. To 10 ml of the filtrate obtained in test A add 3 ml of ammonium chloride (100 g/l)TS and 1 ml of ammonia (~260 g/l)TS; a gelatinous white precipitate is produced.
- C. Using a copper wire mix 0.25 g with about 10 mg of sodium fluoride R placed in a lead or platinum crucible, and add a few drops of sulfuric acid (~1760 g/l)TS to obtain a thin slurry. Cover the crucible with a thin, transparent plastic plate from which a drop of water is suspended and warm gently; a white ring is produced around the drop of water within a short time.

Acid-soluble substances. To 5.0 g add 7.5 ml of hydrochloric acid (~70 g/l)TS and 27.5 ml of water, and boil for 5 minutes. Filter, wash the residue with water and dilute the combined filtrate and washings with sufficient water to produce 50 ml. (Keep the remaining solution for the test for heavy metals). To 10 ml add 1.5 ml of sulfuric acid (~100 g/l)TS, evaporate to dryness on a water-bath, ignite and weigh; the residue weighs not more than 10 mg (10 mg/g).

Heavy metals. To 5 ml of the solution prepared for the test for acid-soluble substances add 5 ml of water, 10 ml of hydrochloric acid (~420 g/l)TS and 25 ml of methylisobutylketone R. Shake for 2 minutes, allow to separate and evaporate the aqueous layer to dryness on a water-bath. Dissolve the residue in 1 ml of acetic acid (~300 g/l)TS and dilute to 40 ml with water. Proceed with the determination of the content as described under "Limit test for heavy metals", Method A; not more than 50 µg/g.

Iron. Triturate 2 g in a mortar with 10 ml of water and add 0.5 g of sodium salicylate R; not more than a slight red tint is observed in the mixture.

Loss on ignition. Ignite to constant weight between 550 and 600 °C; it loses not more than 150 mg/g.

Acidity or alkalinity. To 1.0 g add 20 ml of carbon-dioxide-free water R, shake for 2 minutes and filter. To 10 ml of the filtrate add 0.1 ml of phenolphthalein/ethanol TS; the solution is colourless. Titrate with sodium hydroxide (0.01 mol/l)VS; not more than 0.25 ml is required to obtain a pink colour.

Swelling power. Triturate 2 g with 2 ml of water; the mixture does not flow.

Addition requirements for Kaolin intended for internal use

Heavy metals. To 10 ml of the solution prepared for the test for acid-soluble substances add 10 ml of water, 20 ml of hydrochloric acid (~420 g/l)TS and 25 ml of methylisobutylketone R. Shake for 2 minutes, allow to separate and evaporate the aqueous layer to dryness on a water-bath. Dissolve the residue in 1 ml of acetic acid (~300 g/l)TS and dilute to 40 ml with water. Proceed with the determination of the content as described under "Limit test for heavy metals", Method A; not more than 25 µg/g.

MAGNESII STEARAS
Magnesium stearate

Composition. Magnesium stearate consists mainly of magnesium stearate $(C_{17}H_{35}CO_2)_2Mg$ with variable proportions of magnesium palmitate $(C_{15}H_{31}CO_2)_2Mg$ and magnesium oleate $(C_{17}H_{33}CO_2)_2Mg$.

Description. A white, very fine powder of low bulk density; odour, very faint of stearic acid; unctuous and readily adheres to the skin.

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

Category. Tablet and capsule lubricant, glidant, antiadherent.

Storage. Magnesium stearate should be kept in a well-closed container.

Additional information. Attention should be paid to the microbiological quality since magnesium stearate is of natural origin.

REQUIREMENTS

General requirement. Magnesium stearate contains not less than 3.8 % and not more than 5.8 % of magnesium, Mg, calculated with reference to the dried substance.

Identity tests

A. To 5.0 g add 50 ml of ether R, 20 ml of nitric acid (~130 g/l)TS and 20 ml of water. Heat under a reflux condenser until completely dissolved, and allow to cool. Separate the aqueous layer, shake the ether layer with two quantities, each of 4 ml, of water, combine the aqueous layer, wash with 15 ml of ether R and dilute to 50 ml with water (use this aqueous solution for identity test B and the test for chlorides). Evaporate the ether layer to dryness and dry the residue at 105 °C. The congealing point of the residue is not lower than 53 °C. (Keep the residue for the test of acid value of the fatty acids).

B. To 1 ml of the aqueous solution from test A add 1 ml of ammonia (~100 g/l)TS; a white precipitate is formed which dissolves on the addition of 1 ml of ammonium chloride (100 g/l)TS. Add 1 ml of disodium hydrogen phosphate (40 g/l)TS; a white, crystalline precipitate is produced.

Heavy metals. Use 1.0 g for the preparation of the test solution as described under "Limit test for heavy metals", Procedure 4 (vol. 1, p. 119); determine the heavy metals content according to Method A (vol. 1, p. 119); not more than 20 µg/g.

Chlorides. Proceed with 2 ml of the aqueous solution from identity test A as described under "Limit test for chlorides" (vol. 1, p. 116); the chloride content is not more than 0.25 mg/g.

Loss on drying. Dry to constant weight at 105 °C; it loses not more than 60 mg/g.

Acidity or alkalinity. Boil 1.0 g in 20 ml of carbon-dioxide free water R for 1 minute with continuous shaking. Cool and filter. To 10 ml of the filtrate add 2 drops of bromothymol blue/ethanol TS; not more than 0.05 ml of hydrochloric acid (0.1 mol/l)VS or 0.05 ml of sodium hydroxide (0.1 mol/l)VS is required to obtain the midpoint of the indicator (green).

Acid value of the fatty acids (vol. 1, p. 140). Use 0.2 g of the residue obtained in Identity Test A and dissolve it in 25 ml of the prescribed mixture of solvents.

Assay. Heat gently with caution about 0.5 g, accurately weighed, previously dried, and gradually ignite until a residue is obtained. Cool, add 10 ml of hydrochloric acid (~70 g/l)TS and warm on a water-bath for 10 minutes. Dilute with 25 ml of hot water, add sodium hydroxide (~80 g/l)TS until the solution becomes slightly turbid and 10 ml of ammonium chloride buffer, pH 10.0, TS. Proceed with the titration as described under "Complexometric titration" for magnesium (vol. 1, p. 129). Each ml of disodium edetate (0.05 mol/l)VS is equivalent to 1.215 mg of Mg.

POLYSORBATA 20, 60, 80

Polysorbates 20, 60, 80

Composition. Polysorbates are mixtures of partial fatty acid esters of sorbitol and its anhydrides copolymerized with approximately 20 moles of ethylene oxide for each mole of sorbitol and sorbitol anhydride. In Polysorbate 20 the fatty acid is lauric acid which also may contain other fatty acids.

In Polysorbate 60 the fatty acid is stearic acid which also may contain other fatty acids, especially palmitic acid.

In Polysorbate 80 the fatty acid is oleic acid.

Graphic formulas.

Chemical names.

Polysorbate 20:

Polyoxyethylene 20 sorbitan monolaurate; CAS Reg. No. 9005-64-5.

Polysorbate 60:

Polyoxyethylene 20 sorbitan monostearate; CAS Reg. No. 900-67-8.

Polysorbate 80:

Polyoxyethylene 20 sorbitan monooleate; CAS Reg. No. 9005-65-6.

Description. Polysorbates 20 and 80 are oily, yellowish or yellowish brown liquids. Polysorbate 60 is a gelatinous mass appearing as a clear liquid above 25 °C.

Solubility. Polysorbates are miscible with water, ethanol (~750 g/l)TS, methanol R and ethyl acetate R; practically insoluble in fatty oils and in liquid paraffin R.

Category. Nonionic surfactant.

Storage. Polysorbates should be kept in tightly closed containers, protected from light.

Additional information. Relative densities of Polysorbates 20 and 60

d_{20}^{20} = about 1.10; Polysorbate 80 d_{20}^{20} = about 1.08.

REQUIREMENTS

Identity tests

- A. A mixture of 6 volumes of Polysorbates and 4 volumes of water yields a gelatinous mass at room temperature as well as at lower temperatures.
- B. Dissolve 0.10 g in 5 ml of chloroform R, add 0.10 g of potassium thiocyanate R and 0.10 g of cobalt(II) nitrate R. Stir with a glass rod; the solution becomes blue.

Heavy metals. Use 1.0 g for the preparation of the test solution as described under "Limit test for heavy metals", Procedure 3 (vol. 1, p. 118); determine the heavy metals content according to method A (vol. 1, p. 119); not more than 10 µg/g.

Acid value (vol. 1, p. 140). Not more than 2.0.

Hydroxyl value (see item 5). Use method B;

Polysorbate 20: between 96 - 108

Polysorbate 60: between 81 - 96

Polysorbate 80: between 65 - 80

Iodine value (vol. 1, p. 137).

Polysorbates 20 and 60: not more than 5.0.

Polysorbate 80: between 18 - 24.

Saponification value (vol. 1, p. 139).

Polysorbate 20: between 40 - 50.

Polysorbate 60: between 45 - 55.

Polysorbate 80: between 45 - 55.

Reducing impurities. Dissolve 2.0 g in 25 ml of hot water and add 25 ml of sulfuric acid (~100 g/l)TS and 0.10 ml of ferroin TS. Titrate with ceric ammonium nitrate (0.01 mol/l)VS, shaking continuously, until the colour change from red to greenish blue persists for 30 seconds. Repeat the operation without the substance being tested and make any necessary corrections.

Consumption of ceric ammonium nitrate (0.01 mol/l)VS -

for Polysorbates 20 and 60: not more than 2.0 ml,

for Polysorbate 80: not more than 5.0 ml.

Sulfated ash. Weigh about 2.0 g; not more than 2.5 mg/g.

Water. Determine as described under "Determination of water by the Karl Fischer method", method A (vol. 1, p. 135), using about 1.0 g of the substance; the water content is not more than 30 mg/g.

POLYVIDONUM

Polyvidone

Composition. Polyvidone consists of linear polymers of 1-vinyl-2-pyrrolidinone groups, the degree of polymerization of which results in polymers of various molecular masses ranging from about 10 000 to about 700 000.

Other name. Providone, polyvinylpyrrolidone.

Molecular formula. $(C_6H_9NO)_n$

Graphic formula.

Chemical name. 1-Ethenyl-2-pyrrolidinone homopolymer; 1-vinyl-2-pyrrolidinone polymer; CAS Reg. No. 9003-39-8.

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

Solubility. Soluble in water, ethanol (~750 g/l)TS and chloroform R; practically insoluble in ether R.

Category. Tablet binder and coating agent, viscosity-increasing agent.

Storage. Polyvidone should be kept in a tightly closed container.

Labelling. The designation on the container of Polyvidone should state its viscosity.

Additional information. Polyvidone is hygroscopic. It is not necessarily suitable for use as a blood extender. The viscosity of Polyvidone should be indicated on the label.

REQUIREMENTS

General requirements. Polyvidone contains not less than 11.5 % and not more than 12.8 % of nitrogen N, calculated with reference to the anhydrous substance.

Identity tests

A. Dissolve 0.5 g in 5 ml of water, add 10 ml of hydrochloric acid (1 mol/l)VS and 2 ml of potassium dichromate (100 g/l)TS; an orange yellow precipitate is formed.

B. Dissolve 0.1 g in 1 ml of water, add 0.2 ml of 4-dimethylaminobenzaldehyde TS6 and about 0.1 ml of sulfuric acid (~1760 g/l)TS; a pink colour is produced.

Heavy metals. Use 1.0 g for the preparation of the test solution as described under "Limit test for heavy metals", Procedure 1 (vol. 1, p. 118); determine the heavy metals content according to Method A (vol. 1, p. 119); not more than 10 µg/g.

Sulfated ash. Not more than 1.0 mg/g.

Water. Determine as described under "Determination of water by the Karl Fischer method", Method A (vol. 1, p. 135), using about 0.5 g of the substance; the water content is not more than 50 mg/g.

Aldehydes. To 10 g, accurately weighed, add 180 ml of sulfuric acid (~440 g/l)TS and boil under a reflux condenser for 45 minutes. Cool, re-assemble the apparatus, distil and collect 100 ml of distillate in a flask that is placed in an ice-bath and contains 20 ml of hydroxylamine hydrochloride (70 g/l)TS previously adjusted to pH 3.1. Titrate the distillate with sodium hydroxide (0.1 mol/l)VS to pH 3.1. Repeat the operation without the substance being examined and make any necessary corrections. Each ml of sodium hydroxide (0.1 mol/l)VS is equivalent to 4.405 mg of aldehyde, calculated as acetaldehyde. Not more than 4.6 ml of sodium hydroxide (0.1 mol/l)VS is required (2.0 mg/g).

Vinylpyrrolidinone. Dissolve 10 g, accurately weighed, in 80 ml of water, add 1.0 g of sodium acetate R and titrate with iodine (0.05 mol/l)VS until a persistent colour is obtained. Add an excess of 3.0 ml of iodine (0.05 mol/l)VS, allow to stand for 10 minutes and titrate the excess iodine with sodium thiosulfate (0.1 mol/l)VS adding starch TS towards the end of the titration. Repeat the operation without the substance being examined and make any necessary corrections. Not more than 3.6 ml of iodine (0.05 mol/l)VS is required (2.0 mg/g).

Assay. Carry out Method A as described under "Determination of nitrogen" (vol. 1, p. 136), using about 0.3 g, accurately weighed, and 11 ml of nitrogen-free sulfuric acid (~1760 g/l)TS. To destroy the organic substance carefully add 1 ml of hydrogen peroxide (~330 g/l)TS down the wall of the flask, repeating this addition three to six times, and continue to heat until a clear and slightly green solution is produced. Proceed with the distillation as described. Repeat the operation without the substance being examined. Each ml of sulfuric acid (0.05 mol/l)VS is equivalent to 1.401 mg of N.

SACCHARINUM NATRICUM

Saccharin Sodium

Molecular formula. $C_7H_4NNaO_3S$ (anhydrous); $C_7H_4NNaO_3S \cdot 2H_2O$ (dihydrate).

Relative molecular mass. 205.2 (anhydrous); 241.2 (dihydrate).

Graphic formula.

Chemical name. 1,2-Benzisothiazolin-3(2H)-one, 1,1-dioxide sodium salt; 1,2-benzisothiazolin-3-one 1,1-dioxide sodium salt; CAS Reg. No. 128-44-9 (anhydrous). 1,2-Benzisothiazolin-3(2H)-one, 1,1-dioxide, sodium salt, dihydrate; 1,2-benzisothiazolin-3-one 1,1-dioxide sodium salt dihydrate; CAS Reg. No. 6155-57-3 (dihydrate).

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

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

Category. Sweetening agent.

Storage. Saccharin sodium should be kept in a well-closed container.

Additional information. Saccharin sodium slowly effloresces in air and loses about half the amount of water of crystallization. It has an intensely sweet taste, even in very dilute solutions.

REQUIREMENTS

General requirement. Saccharin sodium contains not less than 98.0 % and not more than 101.0 % of $C_7H_4NNaO_3S$, calculated with reference to the anhydrous substance.

Identity tests

A. Mix 20 mg with 0.04 g of resorcinol R, add about 0.5 ml of sulfuric acid (~1760 g/l)TS and heat gently until a dark green colour is observed. Allow to cool, add 10 ml of water and 10 ml of sodium hydroxide (~80 g/l)TS; a fluorescent green solution is produced.

B. Ignite 1 g of the substance and proceed with the residue as follows:

(a) Dissolve half of the residue in acetic acid (~60 g/l)TS. When tested for sodium as described under "General identification tests" (vol. 1, p. 115) it yields reaction B.

(b) Dissolve the remaining residue in hydrochloric acid (~70 g/l)TS. It yields reaction A described under "General identification tests" as characteristic of sulfates (vol. 1, p. 115).

Water. Determine as described under "Determination of water by the Karl Fischer method", Method A (vol. 1, p. 135), using about 1 g of the substance; the water content is not more than 150 mg/g.

Free acid or alkali. Dissolve 1 g in 10 ml of carbon-dioxide-free water R, add 5 ml of sulfuric acid (0.005 mol/l)VS, boil, cool and titrate with sodium hydroxide (0.01 mol/l)VS using phenolphthalein/ethanol TS as indicator; 4.5 - 5.5 ml of sodium hydroxide (0.01 mol/l)VS is required to obtain a pink colour.

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 100 volumes of chloroform R, 50 volumes of methanol R and 10 volumes of ammonia (~260 g/l)TS as the mobile phase. Apply separately to the plate 5 μ l of each of the following 4 solutions: for solution (A) dissolve 2.6 g of the test substance in 10 ml of sodium hydrogen carbonate (100 g/l)TS, add 12.5 g of white diatomaceous filter-aid and mix well. Transfer to a chromatographic tube, 250 mm in length and with a diameter of 25 mm, at the lower end fitted with a fritted glass disc and a stopcock. Pack

the contents of the tube by tapping on a padded surface and tamping firmly from the top. Elute with dichloromethane R at a rate of 50 ml in about 30 minutes. Evaporate the eluate to dryness and dissolve the residue in 4.0 ml of acetone R. Further prepare solution (B) 50 µg of toluene-2-sulfonamide RS per ml of acetone R, (C) 5 mg of the test substance per ml of methanol R and (D) 50 µg of 4-sulfamoylbenzoic acid R per ml of acetone R. After removing the plate from the chromatographic chamber, dry in a current of warm air, heat at 105 °C for 5 minutes and spray the hot plate with sodium hypochlorite TS1. Dry in a current of cold air until a sprayed area of the plate below the line of application gives at most a faint blue colour with 0.05 ml of a solution containing 5 mg of potassium iodide R in 1 ml of starch TS and 10 µl of glacial acetic acid R. Avoid prolonged exposure to cold air. Spray the plate again with the same mixture. Any spot obtained with solution A corresponding to toluene-2-sulfonamide is not more intense than that obtained with solution B. Any spot obtained with solution C corresponding to 4-sulfamoylbenzoic acid is not more intense than that obtained with solution D.

Assay. Dissolve about 0.3 g, accurately weighed, in 30 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). Each ml of perchloric acid (0.1 mol/l)VS is equivalent to 20.52 mg of $C_7H_4NNaO_3S$.

TALCUM

Talc

Composition. Talc is a powdered, natural hydrate magnesium silicate that may contain variable proportions of aluminium and iron.

Description. A very fine, homogeneous, white or almost white powder; odourless; unctuous and readily adheres to the skin.

Solubility. Practically insoluble in water, in dilute solutions of acids and alkali hydroxides, ethanol (~750 g/l)TS and ether R.

Category. Tablet and capsule lubricant, glidant, diluent.

Storage. Talc should be kept in a well-closed container.

Additional information. Attention should be paid to the microbiological quality since talc is of natural origin.

REQUIREMENTS

Identity tests

A. Mix in a metal crucible 0.5 g with 1 g of potassium nitrate R and 3 g of anhydrous sodium carbonate R, and heat until melted. Allow to cool, add 20 ml of boiling water, mix and filter. Wash the filter with 50 ml of water. Take up the residue with a mixture of 0.5 ml of hydrochloric acid (~420 g/l)TS and 5 ml of water and filter. To the filtrate add 1 ml of ammonia (~260 g/l)TS and 1 ml of ammonium chloride (100 g/l)TS and filter. To the filtrate add 1 ml of disodium hydrogen phosphate (100 g/l)TS; a white, crystalline precipitate is produced.

B. Using a copper wire mix 0.1 g with about 10 mg of sodium fluoride R placed in a lead or platinum crucible, and add a few drops of sulfuric acid (~1760 g/l)TS to obtain a thin slurry. Cover the crucible with a thin transparent plastic plate from which a drop of water is suspended and warm gently; a white ring is produced around the drop of water within a short time.

Microscopic examination. Irregular plates, length up to 50 μ m are observed. It should be free from microscopic asbestos fibres. A 1 mg/ml solution of methylthioninium chloride R in ethanol (~750 g/l)TS does not notably stain the particles.

Arsenic and heavy metals. Transfer 10 g to a 250-ml flask and add 50 ml of hydrochloric acid (0.5 mol/l)VS, attach a reflux condenser and heat on a water-bath for 30 minutes. Cool, transfer the mixture to a beaker, allow the undissolved material to settle. Decant the supernatant liquid through a thick, strong, medium-speed filter-paper into a 100-ml volumetric flask, retaining the undissolved material as much as possible in the beaker. Wash the beaker with three 10-ml portions of hot water, decanting each washing through the same filter. Finally, wash the filter with 15 ml of hot water, cool the filtrate and dilute to volume, and mix. Use this solution for the following limit tests.

Arsenic - Use 10 ml and proceed as described under "Limit test for arsenic" (vol. 1, p. 122); the arsenic content is not more than 3 μ g/g.

Heavy metals - Use 5 ml and proceed as described under "Limit test for heavy metals", Procedure 1 (vol. 1, p. 118); determine the heavy metals content according to Method A (vol. 1, p. 119); not more than 40 μ g/g.

Carbonates. Suspend 0.25 g in 40 ml of sulfuric acid (~100 g/l)TS; no effervescence is observed.

Acid-soluble substances. Digest 1.0 g with 20 ml of hydrochloric acid (~70 g/l)TS at 50 °C for 15 minutes, cool and add sufficient water to produce 50 ml. Filter, centrifuge the filtrate if not clear, to 25 ml of the clear solution (keep the remaining filtrate for the test "Water soluble iron"), add 1 ml of sulfuric acid (~100 g/l)TS and evaporate to dryness. Ignite the residue at 800 ± 25 °C and weigh; not more than 20 mg/g.

Iron. Acidify 10 ml of the filtrate obtained in the test above for "Acid-soluble substances" with hydrochloric acid (~70 g/l)TS and add 1 ml of potassium ferrocyanide (45 g/l)TS; no blue colour is observed.

Reaction and soluble substances. Boil 10 g with 50 ml of water for 30 minutes, adding water from time to time to maintain approximately the original volume and filter; the filtrate is neutral to litmus paper R. Evaporate 20 ml of the filtrate to dryness and dry the residue at 105 °C for 1 hour; the weight of the residue does not exceed 4 mg (1 mg/g).

Loss on ignition. Ignite 1.0 g at 1000 °C to constant weight; it loses not more than 65 mg/g.

3. Unresolved problems

Water for Injections

The Secretariat received the following suggestions:

- a. a reverse osmosis may be recognized as a method of choice in the preparation of Water for Injections;
- b. the LAL-test for bacterial endotoxins could replace the classical pyrogen test in this monograph.

Comments are invited with regard to the above matters.

4. Reagents

Ammonium chloride TS (Nessler's).

Procedure. Dissolve 3.15 g of ammonium chloride R in a sufficient quantity of ammonia-free water R to produce 1000 ml.

Ammonium chloride, dilute, TS (Nessler's).

Procedure. Mix 10 ml of ammonium chloride TS (Nessler's) with a sufficient quantity of ammonia-free water R to produce 1000 ml.

Ceric ammonium nitrate (0.01 mol/l)VS.

Procedure. Dissolve 5.482 g of ceric ammonium nitrate R in sufficient nitric acid (1 mol/l)VS to produce 1000 ml, and filter.

Method of standardization. Ascertain the exact concentration of the 0.01 mol/l solution in the following manner: Measure accurately 2.0 ml of freshly standardized ferrous ammonium sulfate (0.1 mol/l)VS into a flask and dilute with water to about 100 ml. Add 1 drop of nitrophenanthroline TS, and titrate with the ceric ammonium nitrate solution to a colourless endpoint. From the volume of ferrous ammonium sulfate (0.1 mol/l)VS taken and the volume of ceric ammonium nitrate solution consumed, calculate the molarity.

4-Dimethylaminobenzaldehyde TS6.

Procedure. Dissolve 0.2 g of 4-dimethylaminobenzaldehyde R in 20 ml of ethanol (~750 g/l)TS and add 0.5 ml of hydrochloric acid (~420 g/l)TS. Shake the solution with charcoal R and filter. The colour of this test solution is less intense than that of iodine (0.0001 mol/l)VS.

Note: 4-Dimethylaminobenzaldehyde TS6 must be freshly prepared.

Disodium edetate RS. International Chemical Reference Substance.

Ferroin TS.

Procedure. Dissolve 150 mg of o-phenanthroline R in 10 ml of a solution of ferrous sulfate R, prepared by dissolving 700 mg of clear crystals of ferrous sulfate R in 100 ml of water. The ferrous sulfate solution must be prepared immediately before dissolving the o-phenanthroline.

Storage. Store in well-closed containers.

Ferrous sulfate (7 g/l)TS. A solution of ferrous sulfate R in freshly boiled and cooled water containing about 7 g of FeSO_4 per litre.

Note: Ferrous sulfate (7 g/l)TS must be freshly prepared.

Hydroxylamine hydrochloride (70 g/l)TS.

Procedure. Dissolve 69.5 g of hydroxylamine hydrochloride R in sufficient water to produce 1000 ml; 1 mol/l.

Iodine (0.0001 mol/l)VS. Iodine R and potassium iodide R, dissolved in water to contain 25.38 mg of I and 0.36 g of KI in 1000 ml.

Method of standardization. Ascertain the exact concentration of the solution following the method described under iodine (0.1 mol/l)VS.

Lead nitrate (0.1 mol/l)VS. Lead nitrate R, dissolved in water to contain 33.12 g of $\text{Pb}(\text{NO}_3)_2$ in 1000 ml.

Method of standardization. Ascertain the exact concentration of the solution following the method described under lead nitrate (0.05 mol/l)VS, vol. 1, p. 187.

Nitric acid (1 mol/l)VS. Nitric acid (~1000 g/l)TS, diluted with water to contain 63.10 g of HNO_3 in 1000 ml.

Method of standardization. Ascertain the exact concentration of the 1 mol/l solution in the following manner: dissolve 2 g of anhydrous sodium carbonate R in 50 ml of water and titrate with the nitric acid solution using 0.1 ml of methyl orange/ethanol TS as indicator until the solution just becomes reddish yellow. Boil for 2 minutes. The solution reverts to yellow. Cool and continue the titration until the reddish yellow colour is restored. Each ml of nitric acid (1 mol/l)VS is equivalent to 0.0530 g of Na_2CO_3 .

Nitrophenanthroline R. 5-Nitro-1,10-phenanthroline, $\text{C}_{12}\text{H}_7\text{N}_3\text{O}_2$.

Description. A white powder; odourless.

Solubility. Soluble in water.

Melting range (vol. 1, p. 23). 198 - 200 °C.

Nitrophenanthroline TS.

Procedure. Dissolve 150 mg of nitrophenanthroline R in 15 ml of freshly prepared ferrous sulfate (7 g/l)TS.

Opalescence standard TS3.

Procedure. Dilute 10 ml of opalescence standard TS1 with sufficient water to produce 100 ml. Mix well and shake before use.

Note: Opalescence standard TS3 must be freshly prepared.

Phenol (50 g/l)TS. A solution of phenol R containing about 50 g of C_6H_6O per 1000 ml.

Phosphomolybdic acid (80 g/l)TS. A solution of phosphomolybdic acid R containing about 100 g of $H_3PO_4, 12MoO_3, 24H_2O$ per litre.

Pyridine/acetic anhydride TS.

Procedure. Mix 3 volumes of freshly distilled pyridine R with 1 volume of freshly distilled acetic anhydride R.

Note: Pyridine/acetic anhydride TS must be freshly prepared.

Sodium hydrogen carbonate (100 g/l)TS. A solution of sodium hydrogen carbonate R containing about 100 g of $NaHCO_3$ in 1000 ml.

4-Sulfamoylbenzoic acid R. $C_7H_7NO_4S$.

Melting point (vol. 1, p. 23). About 291 °C.

Sulfuric acid (~440 g/l)TS.

Procedure. Dilute 485 ml of sulfuric acid (~1760 g/l)TS to 1000 ml with water, ~4.5 mol/l; d ~1.25.

Toluene-2-sulfonamide RS. International Chemical Reference Substance.

5. New general method

HYDROXYL VALUE

The hydroxyl value of a substance is the number of mg of potassium hydroxide required to neutralize the acid combined by acetylation in 1 g of the substance.

RECOMMENDED PROCEDURES

Method A

To the quantity of the substance being examined indicated in the individual monograph add 12 g of stearic anhydride R and 10 ml of xylene R and heat gently under a reflux condenser for 30 minutes. Allow to cool, add a mixture of 40 ml of pyridine R and 4 ml of water, and heat again under a reflux condenser for 30 minutes. Titrate the hot solution with carbonate-free sodium hydroxide (1 mol/l)VS, using phenolphthalein/ethanol TS as indicator. Repeat the operation without the substance being examined.

Calculate the hydroxyl value from the expression $56.10 \frac{y}{x}$, where y is the difference, in ml, between the titrations and x is the quantity, in g, of the substance taken.

Method B

Unless otherwise indicated in the individual monograph, weigh accurately the quantity of the substance to be examined shown in the table below, place it in a 150-ml acetylation flask fitted with an air condenser and add the corresponding volume of pyridine/acetic anhydride TS.

| Presumed hydroxyl value | Quantity of substance in g | Volume of pyridine/acetic anhydride TS in ml |
|-------------------------|----------------------------|--|
| 10 - 100 | 2.0 | 5.0 |
| 100 - 150 | 1.5 | 5.0 |
| 150 - 200 | 1.0 | 5.0 |
| 200 - 250 | 0.75 | 5.0 |
| 250 - 300 | 0.60 or 1.20 | 5.0 or 10.0 |
| 300 - 350 | 1.0 | 10.0 |
| 350 - 700 | 0.75 | 15.0 |
| 700 - 950 | 0.5 | 15.0 |

Heat the flask for 1 hour in a water-bath, maintaining the level of the water 2-3 cm above the level of the liquid in the flask. Remove the flask and condenser, allow to cool, and add 5 ml of water through the top of the condenser. If a cloudiness appears add sufficient pyridine R to produce a clear liquid, noting the volume added. Shake the flask, place it in a water-bath for 10 minutes, remove and allow to cool. Rinse the condenser and the walls of the flask with 5 ml of neutralized sthanol TS. Titrate with potassium hydroxide/ethanol (0.5 mol/l)VS, using 0.2 ml of phenolphthalein/ethanol TS as indicator. Repeat the operation without the substance being examined.

Calculate the hydroxyl value from the expression $(\underline{a} + 28.05)\underline{v}/\underline{w}$, where \underline{v} is the difference, in ml, between the titrations, \underline{a} is the Acid Value determined for the substance, and \underline{w} is the quantity, in g, of the substance taken.

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