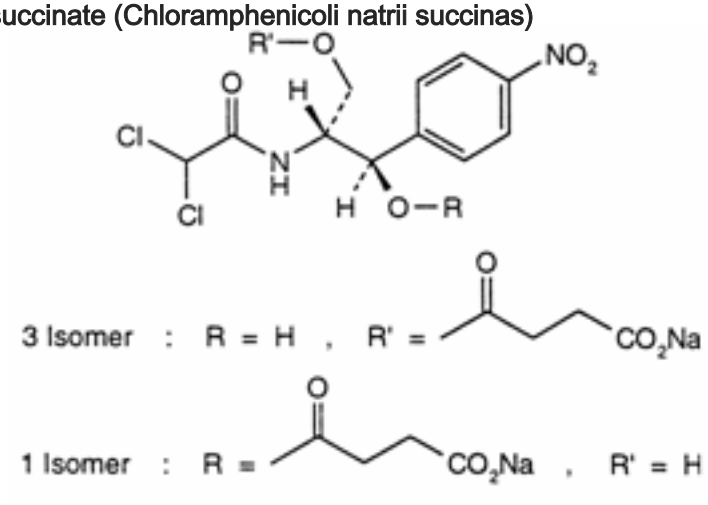
Chloramphenicol sodium succinate (Chloramphenicoli natrii succinas)



$C_{15}H_{15}Cl_2N_2NaO_8$

Relative molecular mass. 445.2

Chemical name. A mixture in variable proportions of (2*R*,3*R*)-2-(2,2- dichloroacetamido)-3-hydroxy-3-(4-nitrophenyl)propyl succinate (3 isomer) and of sodium (1*R*,2*R*)-2-(2,2-dichloroacetamido)-3-hydroxy-1-(4-nitrophenyl) propyl succinate (1 isomer); [*R*-(*R**,*R**)]-mono[2-[(2,2-dichloroacetyl)amino]-3-hydroxy-3-(4-nitrophenyl)propyl] ester, butanedioic acid, monosodium salt; D-*threo*-(-)-2,2-dichloro-*N*-[β-hydroxy-α-(hydroxymethyl)-*p*-nitrophenethyl] acetamide α-(sodium succinate); CAS Reg. No. 982-57-0.

Description. A white or yellowish white powder.

Solubility. Very soluble in water; freely soluble in ethanol (~750 g/l)TS.

Category. Antibacterial drug.

Storage. Chloramphenicol sodium succinate should be kept in a tightly closed container, protected from light.

Labelling. The designation Chloramphenicol sodium succinate for parenteral use indicates that the substance complies with the additional requirements and may be used for parenteral administration. Expiry date.

Additional information. Chloramphenicol sodium succinate is hygroscopic. Even in the absence of light, Chloramphenicol sodium succinate gradually degrades when exposed to a humid atmosphere; decomposition is more rapid at higher temperatures.

Requirements

Chloramphenicol sodium succinate contains not less than **98.0%** and not more than the equivalent of **102.0%** of $C_{15}H_{15}Cl_2N_2NaO_8$, calculated with reference to the anhydrous substance.

Identity tests

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

B. See the test described below under "Chloramphenicol and chloramphenicol disodium disuccinate, test B". The two principal spots obtained with solution A correspond in position and appearance with those obtained with solution B. The positions of the spots obtained with solutions A and B are different from that of the principal spot obtained with solution C.

C. Dissolve 10 mg in 2.0 mL of ethanol (~750 g/l) TS, add 0.2 g of zinc R powder, 1.0 mL of sulfuric acid (~100 g/l) TS, and allow to stand for 10 minutes. Filter. To the filtrate add 0.5 mL of sodium nitrite (10 g/l) TS, and allow to stand for 2 minutes. Then add 1.0 g of urea R and a solution containing 10mg of 2-naphthol R in 2ml of sodium hydroxide (~80 g/l) TS; a red colour is produced. Repeat the test omitting the zinc R powder; no red colour is produced.

D. Dissolve 5 mg in 5 mL of water and add a few drops of silver nitrate (40 g/l) TS; no precipitate is produced. Heat 0.05g with 2.0ml of potassium hydroxide/ethanol TS1 on a water-bath for 15 minutes, add 15mg of charcoal R, shake, and filter. The filtrate yields reaction A described under 2.1 General identification tests as characteristic of chlorides.

E. When tested for sodium as described under 2.1 General identification tests, it yields the characteristic

reactions. If reaction B is to be used, prepare a 20 mg/mL solution.

Specific optical rotation. Use a 50 mg/mL solution and calculate with reference to the anhydrous substance; $[\alpha]_D^{20\,°C}$ = +5.0° to +8.0°.

Clarity of solution. A solution of 1.0 g in 3.0 mL of carbon-dioxide-free water R is clear.

Water. Determine as described under 2.8 Determination of water by the Karl Fischer method, Method A, using about 0.5 g of Chloramphenicol sodium succinate; the water content is not more than 0.20 g/g.

pH value. pH of a 0.25 g/mL solution in carbon-dioxide-free water R, 6.4-7.0.

Chloramphenicol and chloramphenicol disodium disuccinate

• Either test A or test B may be applied.

A. Carry out the test as described under *1.14.1 Chromatography*, High-performance liquid chromatography, using a stainless steel column (25cm × 4.6mm) packed with particles of silica gel, the surface of which has been modified with chemically bonded octadecylsilyl groups (5µm). As the mobile phase, use a mixture of 55 volumes of water, 40 volumes of methanol R, and 5 volumes of phosphoric acid (~20 g/l) TS.

Prepare the following solutions in the mobile phase: solution (A) 0.25mg of Chloramphenicol sodium succinate per mL; solution (B) 5.0 µg of chloramphenicol RS per mL; solution (C) 5.0 µg of chloramphenicol disodium disuccinate RS per mL; and for solution (D) dissolve 25mg of Chloramphenicol sodium succinate in the mobile phase, add 0.5 mg of chloramphenicol RS and 0.5 mg of chloramphenicol disodium disuccinate RS and dilute to 100ml with the mobile phase.

Operate with a flow rate of 1.0 mL per minute. As a detector use an ultraviolet spectrophotometer set at a wavelength of about 275nm.

Using a 20-µl loop injector inject solution D. Inject alternately solutions A, B, C, and D. The test is not valid unless the two peaks in the chromatogram obtained with solution D, corresponding to those in the chromatograms obtained with solutions B and C, are clearly separated from the peaks corresponding to the two principal peaks in the chromatogram obtained with solution A. If necessary, adjust the methanol content of the mobile phase.

Measure the areas of the peak responses obtained in the chromatograms from solutions A, B, and C, and calculate the content of the related substances as a percentage. In the chromatogram obtained with solution A, the area of any peak corresponding to chloramphenicol is not greater than that of the principal peak obtained with solution B (2.0%). The area of any peak corresponding to chloramphenicol disodium disuccinate is not greater than that of the principal peak obtained with solution C (2.0%).

B. Carry out the test as described under *1.14.1 Chromatography*, Thin-layer chromatography, using silica gel R4 as the coating substance and a mixture of 85 volumes of dichloromethane R, 14 volumes of methanol R, and 1 volume of acetic acid (~60 g/l) TS as the mobile phase. Apply separately to the plate 2 µl of each of 3 solutions in acetone R containing (A) 10mg of Chloramphenicol sodium succinate per mL, (B) 10 mg of chloramphenicol sodium succinate RS per mL, and (C) 10 mg of chloramphenicol RS per mL. Then apply separately 10 µl of solution (A) as prepared above and 1 µl of solution (D) containing 0.20 mg of chloramphenicol RS per mL of acetone R. After removing the plate from the chromatographic chamber, allow it to dry in air until the solvents have evaporated, and examine the chromatogram in ultraviolet light (254 nm).

Any spot obtained with the second application of solution A, other than the principal spot, is not more intense than that obtained with solution D (2.0%).

Assay. Dissolve about 0.2 g, accurately weighed, in sufficient water to produce 500 mL; dilute 5.0 mL of this solution to 100 mL with water. Measure the absorbance of the diluted solution in a 1-cm layer at the maximum at about 276nm and calculate the percentage content of $C_{15}H_{15}Cl_2N_2NaO_8$ using the absorptivity value of 22.0 ($A_{1cm}^{1\%}$ = 220), and with reference to the anhydrous substance.

Additional requirements for Chloramphenicol sodium succinate for parenteral use

Complies with the monograph for "Parenteral preparations".

Storage. Sterile Chloramphenicol sodium succinate should be kept in a sterile, tightly closed, and tamper-evident container, protected from light.

Bacterial endotoxins. Carry out the test as described under 3.4 Test for bacterial endotoxins; contains not more than 0.2 IU of

endotoxin RS per mg.

Sterility. Complies with 3.2 Test for sterility.