Mitotane Capsules

Dissolution <*6.10*> Perform the test with 1 capsule of Mitotane Capsules at 100 revolutions per minute according to the Paddle method, using the sinker, using 900 mL of a solution, prepared by adding 2nd fluid for dissolution test to 1 g of polysorbate 80 to make 100 mL, as the dissolution medium. Start the test, withdraw 20 mL of the medium at the specified minute after starting the test, and immediately fill up the dissolution medium with exactly 20 mL of a solution, prepared by adding 2nd fluid for dissolution test to 1 g of polysorbate 80 to make 100 mL, previously warmed to 37 ± 0.5ºC, carefully. Filter the media through a membrane filter with a pore size not exceeding 0.45 μm. Discard the first 10 mL of the filtrate, pipet *V* mL of the subsequent filtrate, add a solution, prepared by adding 2nd fluid for dissolution test to 1 g of polysorbate 80 to make 100 mL, to make exactly *V′* mL so that each mL contains about 0.56 mg of mitotane ($C_{14}H_{10}Cl_4$) according to the labeled amount, and use this solution as the sample solution. Separately, weigh accurately about 28 mg of Mitotane RS, previously dried under reduced pressure of 3.3 to 6.7 kPa at 60ºC for 3 hours, dissolve the mobile phase to make exactly 50 mL, and use this solution as the standard solution. Perform the test with exactly 10 μL each of the sample solution and standard solution as directed under Liquid Chromatography <*2.01*> according to the following conditions, and determine the peak areas, A_T and A_S, of mitotane of both solutions.

The requirements are met if Mitotane Capsules conform to the dissolution requirements.

Dissolution rate (%) with respect to the labeled amount of mitotane ($C_{14}H_{10}Cl_4$)
on the *n*th dissolution medium withdrawing (*n*=1,2,3)

$$= M_S \times \left\{ \frac{A_{T(n)}}{A_S} + \sum_{i=1}^{n-1} \left(\frac{A_{T(i)}}{A_S} \times \frac{1}{45} \right) \right\} \times \frac{V'}{V} \times \frac{1}{C} \times 1800$$

M_S: Amount (mg) of Mitotane RS

C: Labeled amount (mg) of mitotane ($C_{14}H_{10}Cl_4$) in 1 capsule

Operating conditions—

Detector: An ultraviolet absorption photometer (wavelength: 230 nm).

Column: A stainless steel column 4 mm in inside diameter and 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 25ºC.

Mobile phase: Dissolve 0.27 g of potassium dihydrogen phosphate in water to make 200 mL, and adjust the pH to 5.5 with 0.05 mol/L potassium hydroxide TS. To 200 mL of this solution add 800 mL of acetonitrile.

Flow rate: Adjust the flow rate so that the retention time of mitotane is about 5 minutes.

System suitability−

System performance: When the procedure is run with 10 μL of the standard solution under the above operating conditions, the number of theoretical plates and the symmetry factor of the peak of mitotane are not less than 5000 and not more than 1.5, respectively.

System repeatability: When the test is repeated 6 times with 10 μL of the standard solution under the above operating conditions, the relative standard deviation of the peak area of mitotane is not more than 1.0%.

Dissolution Requirements

Labeled amount	Specified minute	Dissolution rate
500 mg	60 minutes	15−45%
	3 hours	35−65%
	24 hours	Not less than 75%

Mitotane RS $C_{14}H_{10}Cl_4$: 320.04 1,1-dichloro-2-(2-chlorophenyl)-2-(4-chlorophenyl)ethane. It meets the following requirements.

Description−Mitotane RS occurs as white to pale yellowish white crystals.

Identification−Dissolve 50 mg of Mitotane RS in 100 mL of ethanol (95), and use this solution as the sample stock solution. To 2 mL of the sample stock solution add ethanol (95) to make 100 mL, and use this solution as the sample solution (1). To 8 mL of the sample stock solution add ethanol (95) to make 20 mL, and use this solution as the sample solution (2). Determine the absorption spectrum of the sample solution (1) as directed under Ultraviolet-visible Spectrophotometry <*2.24*>: it exhibits a maximum between 228 nm and 231 nm. Also, determine the absorption spectrum of the sample solution (2) as directed under Ultraviolet-visible Spectrophotometry <*2.24*>: it exhibits maxima between 259 nm and 262 nm, between 265 nm and 268 nm, and 273 nm and 276 nm. Determine the absorbances, A_1, A_2 and A_3, at 259 nm and 262 nm, 265 nm and 268 nm, and 273 nm and 276 nm at the wavelength of maximum: the ratio A_1/A_2 is between 0.84 and 0.89 and A_3/A_2 is between 0.66 and 0.71, respectively.

Melting point <*2.60*>: 75 − 79ºC

Related substances−Dissolve about 30 mg of Mitotane RS in 50 mL of acetonitrile, and use this solution as the sample solution. Perform the test with 5 μL of the sample solution as directed under Liquid Chromatography <*2.01*> according to the following conditions. Determine each peak area by the automatic integration method, and calculate the peak areas other than mitotane by the area percentage method: the peak of 1,1-dichloro-2,2-bis(4-chlorophenyl)ethance(*pp'*-DDD), having the

relative retention time of about 0.9 with respect to mitotane, and the peak of 1,1,1-trichloro-2-(2-chlorophenyl)-2-(4-chlorophenyl)ethane(*op'*-DDT), having the relative retention time of about 1.7, are not more than 0.5% and 0.1%, respectively, and the total area of the peaks other than mitotane is not more than 1.0%.

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 230 nm).

Column: A stainless steel column 4 mm in inside diameter and 30 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 25ºC.

Mobile phase: Dissolve 0.27 g of potassium dihydrogen phosphate in water to make 200 mL, and adjust the pH to 5.5 with 0.05 mol/L potassium hydroxide TS. To 200 mL of this solution add 800 mL of acetonitrile.

Flow rate: Adjust the flow rate so that the retention time of mitotane is about 10 minutes.

Time span of measurement: About 3 times as long as the retention time of mitotane beginning after the solvent peak.

System suitability

Test for required detectability: To 1 mL of the sample solution add acetonitrile to make 10 mL. To 1 mL of this solution add acetonitrile to make 50 mL, and use this solution as the solution for system suitability test. Pipet 5 mL of the solution for system suitability test, and add acetonitrile to make exactly 50 mL. Confirm that the peak area of mitotane obtained from 5 μL of this solution is equivalent to 7 to 13% of that from 5 μL of the solution for system suitability test.

System performance: When the procedure is run with 5 μL of the solution for system suitability test under the above operating conditions, the number of theoretical plates and the symmetry factor of the peak of mitotane are not less than 8000 and not more than 1.5, respectively.

System repeatability: When the test is repeated 6 times with 5 μL of the solution for system suitability test under the above operating conditions, the relative standard deviation of the peak area of mitotane is not more than 2.0%.

Loss on drying <*2.41*>: not more than 0.5% (1 g, reduced pressure of 3.3 to 6.7 kPa, 60ºC, 3 hours).

Content: not less than 99.5%. Assay−Weigh accurately about 40 mg of Mitotane RS, previously dried, using a mixture of 0.5 mL of 0.01 mol/L sodium hydroxide TS and 20 mL of water as the absorbing liquid, decompose as directed under Oxygen Flask Combustion Method <*1.06*>, shake well while absorbing a combustion gas, and use this solution as the test solution. Neutralize test solution with diluted 0.2 mol/L sodium hydroxide TS (1 in 2), add 2 mL of nitric acid, 4 mL of nitrobenzene and 2 mL of ammonium iron (III) sulfate TS, add exactly 10 mL of 0.1 mol/L silver nitrate VS, and titrate <*2.50*> the excess silver nitrate with 0.05 mol/L potassium thiocyanate VS until the color of the solution changes to red. Perform a blank determination in the same manner.

Each mL of 0.1 mol/L silver nitrate VS
= 2.000 mg of $C_{14}H_{10}Cl_4$

0.05 mol/L Potassium Thiocyanate VS

1000 mL of this solution contains 4.859 g of potassium thiocyanate (KSCN: 97.18).

Preparation−Dissolve 5 g of potassium thiocyanate in water to make 1000 mL, and standardize the solution as follows:

Standardization−Pipet 10 mL of 0.1 mol/L silver nitrate VS, add 20 mL of water, 2 mL of nitric acid and ammonium iron (III) sulfate TS, and titrate with the prepared potassium thiocyanate VS to the first appearance of a persistent red-brown color with shaking. Calculate the morality factor.

Note: Store protected from light.