Copovidone

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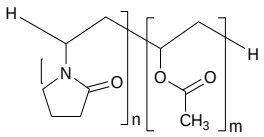

$(C_6H_9NO)_n(C_4H_6O_2)_m$

Poly[(2-oxopyrrolidin-1-yl)ethylene-*co*-(1-acetoxyethylene)]

[*25086-89-9*]

This monograph is harmonized with the European Pharmacopoeia and the U.S. Pharmacopeia.

The corresponding part of the attributes/provisions which are agreed as non-harmonized within the scope of the harmonization is marked with symbols (◆ ◆), and the corresponding parts which are agreed as the JP local requirement other than the scope of the harmonization are marked with symbols (◇ ◇).

Copovidone is a copolymer of 1-vinyl-2-pyrrolidone and vinyl acetate at the ratio by weight of 3:2.

It contains not less than 35.3% and not more than 42.0% of vinyl acetate ($C_4H_6O_2$: 86.09), and not less than 7.0% and not more than 8.0% of nitrogen (N: 14.01), calculated on the dried basis.

The nominal K-value is shown on the label.

◆**Description** Copovidone occurs as a white to yellowish white powder.

It is odorless or has a faint, characteristic odor.

It is very soluble in methanol and in ethanol (95), and freely soluble in water.

It is hygroscopic.◆

Identification Determine the infrared absorption spectrum of Copovidone, previously dried, as directed in the potassium bromide disk method under Infrared Spectrophotometry <*2.25*>, and compare the spectrum with the Reference Spectrum: both spectra exhibit similar intensities of absorption at the same wave numbers.

pH <*2.54*> Dissolve 1.0 g of Copovidone in 10 mL of water: the pH of the solution is between 3.0 and 7.0.

Purity **(1)** Clarity and color of solution－Dissolve 1.0 g of Copovidone in 10 mL of water: the solution is colorless to pale yellow, or pale red, and it is clear or slightly opalescent.

◇**(2)** Heavy metals <*1.07*>－Ignite 2.0 g of Copovidone as directed under Residue on Ignition Test <*2.44*>, add 2 mL of hydrochloric acid to the residue, then proceed according to Method 2, and perform the test. Prepare the control solution with 2.0 mL of Standard Lead Solution (not more than 10 ppm).◇

(3) Aldehydes－Weigh accurately about 1 g of Copovidone, dissolve in 0.05 mol/L pyrophosphate buffer solution (pH 9.0) to make exactly 100 mL. Stopper, heat at 60℃ for 60 minutes, allow to cool to room temperature, and use this solution as the sample solution. Separately, dissolve 0.140 g of acetaldehyde ammonia trimer trihydrate in water to make exactly 200 mL. Pipet 1 mL of this solution, add 0.05 mol/L pyrophosphate buffer solution (pH 9.0) to make exactly 100mL, and use this solution as the standard solution. Measure exactly 0.5 mL each of the sample solution, standard solution and water, transfer to separate 1-cm cells, add 2.5 mL of 0.05 mol/L pyrophosphate buffer solution (pH 9.0) and 0.2 mL of *β*-nicotinamide adenine dinucleotide TS to each of these cells, mix and stopper tightly. Allow to stand for 2 to 3 minutes at 22 ± 2℃, and perform the test with these solutions as directed under Ultraviolet-visible Spectrophotometry <*2.24*> using water as the control solution. Determine the absorbances, A_{T1}, A_{S1} and A_{B1}, of the subsequent solutions of the sample solution, the standard solution and water (blank) at 340 nm. Then, add 0.05 mL of aldehyde dehydrogenase TS to each of the cells, stir, and stopper tightly. Allow to stand at 22±2°C for 5 minutes. Determine the absorbances, A_{T2}, A_{S2} and A_{B2}, of these solutions in the same manner as above: the content of aldehyde is not more than 500 ppm (as acetaldehyde).

Content (ppm) of aldehydes [as acetaldehyde (CH_3CHO)]

$$= C/M \times \{(A_{T2} - A_{T1}) - (A_{B2} - A_{B1})\} / \{(A_{S2} - A_{S1}) - (A_{B2} - A_{B1})\} \times 100{,}000$$

M: Amount (g) of Copovidone taken, calculated on the dried basis

C: Concentration (mg/mL) of acetaldehyde in the standard solution, using 0.72 as conversion factor for acetaldehyde ammonia trimer trihydrate to acetaldehyde

(4) 1-Vinyl-2-pyrrolidone and vinyl acetate－Store the sample solution and standard solution at 5℃ or below, and use within 8 hours. Weigh accurately about 0.25 g of Copovidone, dissolve in a mixture of water and acetonitrile (23:2) to make exactly 10 mL, and use this solution as the sample solution. Separately, dissolve 50 mg each of 1-vinyl-2-pyrrolidone and vinyl acetate in methanol to make exactly 100 mL. Pipet 1 mL of this solution and add methanol to make exactly 100 mL. Pipet 5 mL of this solution, add a mixture of water and acetonitrile (23:2) to make exactly 100 mL, and use this solution as the standard solution. Perform the test with exactly 20 *μ*L each of the sample solution and standard solution as directed under Liquid Chromatography <*2.01*> according to the following conditions, determine the peak areas, A_{Ta}, A_{Tb}, A_{Sa} and A_{Sb}, of 1-vinyl-

2-pyrrolidone and vinyl acetate in each solution, and calculate the content of 1-vinyl-2-pyrrolidone and vinyl acetate by the following equations: they are not more than 10 ppm.

$$\text{Content (ppm) of 1-vinyl-2-pyrrolidone} = A_{Ta} / A_{Sa} \times C_{Sa} / C_T \times 1000$$

$$\text{Content (ppm) of vinyl acetate} = A_{Tb} / A_{Sb} \times C_{Sb} / C_T \times 1000$$

C_{Sa}: Concentration (μg/mL) of 1-vinyl-2-pyrrolidone in the standard solution
C_{Sb}: Concentration (μg/mL) of vinyl acetate in the standard solution
C_T: Concentration (mg/mL) of Copovidone in the sample solution, calculated on the dried basis

Operating conditions—

Detector: An ultraviolet spectrophotometer (wavelength: 235 nm for 1-vinyl-2-pyrrolidone, 205 nm for vinyl acetate).

Column: Two stainless steel columns, one is 4 mm in inside diameter and 33 mm in length and the other is 4 mm in inside diameter and 250 mm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter), and use them as the pre-column and the separation column, respectively.

Column temperature: A constant temperature of about 40℃.

Mobile phase: A mixture of water and acetonitrile (23:2).

Flow rate: 1.0 mL per minute (Retention times of 1-vinyl-2-pyrrolidone and vinyl acetate are about 17 and about 22 minutes, respectively).

Time span of measurement: For 40 minutes.

Washing of column: After each test with the sample solution, elute and wash away remaining sample by passing the mobile phase through the separation column or the pre-column backwards at the flow rate mentioned above for 30 minutes.

System suitability—

System performance: When the procedure is run with 20 μL of the standard solution under the above operating conditions (wavelength: 205 nm), 1-vinyl-2-pyrrolidone and vinyl acetate are eluted in this order with the resolution between these peaks being not less than 2.0.

System repeatability: When the test is repeated 6 times with 20 μL of the standard solution under the above operating conditions, the relative standard deviations of the peak areas of 1-vinyl-2-pyrrolidone and vinyl acetate are not more than 2.0%, respectively.

(5) Peroxides－Weigh exactly an amount of Copovidone, equivalent to 4.0 g calculated on the dried basis, dissolve in water to make exactly 100 mL, and use this solution as the sample solution. To 25 mL of the sample solution add 2 mL of titanium (III) chloride-sulfuric acid TS, and mix. Allow to stand for 30 minutes, and perform the test with this solution as directed under Ultraviolet-visible Spectrophotometry *<2.24>*, using a solution prepared by adding 2 mL of diluted sulfuric acid (13 in 100) to 25 mL of the sample solution as a blank: the absorbance of the sample solution at 405 nm is not more than 0.35 (not more than 400 ppm, as hydrogen peroxide).

(6) Hydrazine－Weigh exactly an amount of Copovidone equivalent to 2.5 g calculated on the dried basis, transfer to a 50-mL centrifuge tube, add 25 mL of water, and stir to dissolve. Add 500 μL of a solution of salicylaldehyde in methanol (1 in 20), stir and warm at 60℃ for 15 minutes in a water bath. Allow to cool, add 2.0 mL of toluene, stopper tightly, shake vigorously for 2 minutes, centrifuge, and use the upper layer of the mixture as the sample solution. Separately, dissolve 90 mg of salicylaldazine in toluene to make exactly 100 mL. Pipet 1 mL of this solution, add toluene to make exactly 100 mL, and use this solution as the standard solution. Perform the test with these solutions as directed under Thin-layer Chromatography *<2.03>*. Spot 10 μL each of the sample solution and standard solution on a plate of dimethylsilanized silica gel with fluorescent indicator for thin-layer chromatography. Develop the plate with a mixture of methanol and water (2:1) to a distance of about three-fourths of the length of the plate, and air-dry the plate. Examine under ultraviolet light (main wavelength: 365 nm): the fluorescence of the spot obtained from the sample solution corresponding to the spot having a *R*f value of about 0.3 from the standard solution is not more intense than that of the spot from the standard solution (not more than 1 ppm).

(7) 2-Pyrrolidone－Weigh accurately about 1 g of Copovidone, add 5 mL of methanol for liquid chromatography, and sonicate to dissolve. Add water to make exactly 100 mL, and use this solution as the sample solution. Separately, dissolve 0.150 g of 2-pyrrolidone in a mixture of water and methanol for liquid chromatography (19:1) to make exactly 100 mL. Pipet 3 mL of this solution, add a mixture of water and methanol for liquid chromatography (19:1) to make exactly 100 mL, and use this solution as the standard solution. Perform the test with exactly 20 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 2-pyrrolidone in each solution. Calculate the content of 2-pyrrolidone by the following equation: not more than 0.5%.

$$\text{Content (\%) of 2-pyrrolidone} = A_T / A_S \times C_S / C_T \times 100$$

C_S: Concentration (mg/mL) of 2-pyrrolidone in the standard solution
C_T: Concentration (mg/mL) of Copovidone in the sample solution, calculated on the dried basis

Operating conditions—

Detector: An ultraviolet absorption photometer (wavelength: 205 nm).

Column: Two stainless steel columns, one is 4.0 mm in inside diameter and 10 mm in length and the other is 4.6 mm in inside diameter and 150 mm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter), and use them as the pre-column and the separation column, respectively.

Column temperature: A constant temperature of about 40℃.

Mobile phase: A mixture of water and methanol for liquid chromatography (19:1).

Flow rate: 0.8 mL per minute (retention time of 2-pyrrolidone is about 7 minutes).

Time span of measurement: For 30 minutes.

Washing of column: After each test with the sample solution, elute and wash away remaining sample by passing the mobile phase through the separation column or the pre-column backwards at the flow rate mentioned above for 30 minutes.

System suitability—

System performance: When the procedure is run with 20 μL of the standard solution under the above operating conditions, the number of theoretical plates and the symmetry factor of the peak of 2-pyrrolidone are not less than 5000 and not more than 1.5, respectively.

System repeatability: When the test is repeated 6 times with 20 μL of the standard solution under the above operating conditions, the relative standard deviation of the peak area of 2-pyrrolidone is not more than 2.0%.

Loss on drying <*2.41*> Not more than 5.0% (0.5 g, 105℃, 3 hours).

Residue on ignition <*2.44*> Not more than 0.1% (1 g).

K-value Weigh exactly an amount of Copovidone, equivalent to 1.000 g, calculated on the dried basis, dissolve in water to make exactly 100 mL, allow to stand for 60 minutes, and use this solution as the sample solution. Perform the test with the sample solution and with water at 25℃ as directed in Method 1 under the Viscosity Determination <*2.53*>, and calculate the K-value by the following formula: the K-value of Copovidone is not less than 90.0% and not more than 110.0% of the nominal K-value.

$$K=\frac{1.5\log v_{rel.}-1}{0.15+0.003c}+\frac{\sqrt{300c\log v_{rel.}+(c+1.5c\log v_{rel.})^2}}{0.15c+0.003c^2}$$

c: Mass (g) of Copovidone in 100 mL of the solution, calculated on the dried basis
$v_{rel.}$: Kinematic viscosity of the sample solution relative to that of water

Assay (1) Vinyl acetate—Weigh accurately about 2 g of Copovidone, add exactly 25 mL of 0.5 mol/L potassium hydroxide-ethanol TS and a few glass beads, heat under reflux for 30 min. Titrate immediately with 0.5 mol/L hydrochloric acid VS (indicator: 1 mL of phenolphthalein TS). Perform a blank determination in the same manner, and make any necessary correction.

$$\text{Amount (\%) of vinyl acetate}=0.1\times\frac{86.09}{56.11}\times\frac{28.05\,(n_2-n_1)}{M}$$

M: Amount (g) of Copovidone taken, calculated on the dried basis
n_1: Volume (mL) of 0.5 mol/L hydrochloric acid VS consumed in the blank test
n_2: Volume (mL) of 0.5 mol/L hydrochloric acid VS consumed in the test

(2) Nitrogen—Weigh accurately about 0.1 g of Copovidone, and place in a Kjeldahl flask. Add 5 g of a powdered mixture of 33 g of potassium sulfate, 1 g of copper (II) sulfate pentahydrate and 1 g of titanium (IV) oxide, and wash down any adhering sample from the neck of the flask with a small amount of water. Add 7 mL of sulfuric acid allowing to flow down the inside wall of the flask. Heat the flask gradually until the solution has a clear, yellow-green color, and the inside wall of the flask is free from a carbonized material, and then heat for further 45 minutes. After cooling, add cautiously 20 mL of water, and connect the flask to the distillation apparatus previously washed by passing steam through it. To the absorption flask add 30 mL of a solution of boric acid (1 in 25), 3 drops of bromocresol green-methyl red TS and sufficient water to immerse the lower end of the condenser tube. Add 30 mL of a solution of sodium hydroxide (2 in 5) through the funnel, rinse cautiously the funnel with 10 mL of water, immediately close the clamp attached to the rubber tube, then start the distillation with steam to obtain 80 to 100 mL of the distillate. Remove the absorption flask from the lower end of the condenser tube, rinsing the end part with a small quantity of water, and titrate <*2.50*> the distillate with 0.025 mol/L sulfuric acid VS until the color of the solution changes from green through pale grayish blue to pale grayish red-purple. Perform a blank determination in the same manner, and make any necessary correction.

290 Each mL of 0.025 mol/L sulfuric acid VS = 0.700 mg of N

291 ◆**Containers and storage** Containers—Tight containers.

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