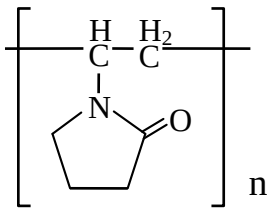
Povidone
(Rev. 1, Stage 4)

Polyvidone
Polyvinylpyrrolidone



$(C_6H_9NO)_n$ [*9003-39-8*]
Poly [(2-oxo-1-pyrrolidinyl) ethylene]

Povidone is a chain polymer of 1-vinyl-2-pyrrolidone. It contains not less than 11.5% and not more than 12.8% of nitrogen (N: 14.01), calculated on the anhydrous basis.
It has the nominal K-value of not less than 10 and not more than 120.
The nominal K-value is shown on the label.

Identification:
(1) To 0.5 g of Povidone, add 10 ml of water, and shake. The substance dissolves.

pH Dissolve 1.0 g of Povidone in 20 mL of water: the pH of this solution is between 3.0 and 5.0 for Povidone having the nominal K-value of 30 or less, and between 4.0 and 7.0 for Povidone having the nominal K-value exceeding 30.

Purity
(1) Aldehydes – Weigh accurately about 1.0 g of Povidone, and dissolve in 0.05 mol/L pyrophosphate buffer solution, pH 9.0 to make exactly 100 mL. Stopper tightly, warm at 60°C for 60 minutes, allow to cool to room temperature, and use this solution as the sample solution. Separately, prepare the standard solution as follows: dissolve 0.140 g of acetaldehyde ammonia trimer trihydrate in water to make 200.0 mL, dilute 1.0 mL of the solution to 100.0 mL with 0.05 mol/L pyrophosphate buffer solution, pH 9.0.
Measure exactly 0.5 mL each of the sample solution, the standard solution and water (for blank test), transfer to separate cells with a path length of 1 cm, 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°C, and perform the test with these solutions as directed under the Spectrophotometry 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 aldehydes is not more than 500 ppm (as acetaldehyde).

$$\text{Content (ppm) of aldehydes as acetaldehyde} = \frac{(A_{t2}-A_{t1})-(A_{b2}-A_{bl})}{(A_{s2}-A_{s1})-(A_{b2}-A_{bl})} \times \frac{W'}{W} \times 100000$$

W: Weighed amount (g) of Povidone, calculated on the anhydrous basis.

W': Concentration (mg/mL) of acetaldehyde in the standard solution, calculated from the weight of the acetaldehyde ammonia trimer trihydrate with the factor 0.72.

(2) 1-Vinyl-2-pyrrolidone—Weigh accurately about 0.25 g of Povidone, dissolve in a mixture of acetonitrile and water [10 : 90 (v : v)] to make exactly 10 mL, and use this solution as the sample solution. Separately, dissolve 0.050 g of 1-vinyl-2-pyrrolidone in a mixture of acetonitrile and water [10 : 90 (v : v)] to make exactly 100mL. Pipet 1 mL of this solution and add a mixture of acetonitrile and water [10 : 90 (v : v)] to make exactly 100 mL. Pipet 5 mL of this solution and add a mixture of acetonitrile and water [10 : 90 (v : v)] 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 the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the peak areas, A_T and As, of 1-vinyl-2-pyrrolidone in each solution: the content of 1-vinyl-2- pyrrolidone is not more than 10 ppm.

$$\text{Content (ppm) of 1-vinyl-2-pyrrolidone} = \frac{A_T}{A_S} \times \frac{2.5}{W}$$

W: Weighed amount (g) of Povidone, calculated on the anhydrous basis.

Operating conditions –

Detector: An ultraviolet spectrophotometer (detection wavelength: 235 nm)

Column: Stainless steel column 4.0 mm in inside diameter and about 10 mm in length, and 4.6 mm in inside diameter and about 150 mm in length, packed with

octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter), and use them as a guard column and a separation column, respectively.

Column temperature: A constant temperature of about 40°C.
Mobile phase: Acetonitrile : water [10 : 90 (v : v)] .
Flow rate: 1.0 mL/min
Selection of column: Dissolve 0.01 g of 1-vinyl-2-pyrrolidone and 0.5 g of vinyl acetate in 100 mL of methanol. To 1 mL of this solution add a mixture of acetonitrile and water [10 : 90 (v : v)] to make 100 mL. Proceed with 50 μL of this solution according to the above operating conditions. Use a column giving elution of 1-vinyl-2-pyrrolidone and vinyl acetate in this order with the resolution between their peaks being not less than 2.0.
System reproducibility: When the test is repeated six times with the standard solution under the above operating conditions, the relative standard deviation of obtained peak areas of 1-vinyl-2-pyrrolidone is not more than 2.0%.

(3) Peroxides – Weigh exactly an amount of Povidone, equivalent to 4.0 g calculated on the anhydrous 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 the Spectrophotometry, using a solution prepared by adding 2 mL of 13% sulfuric acid to 25 mL of the sample solution as a blank: the absorbance of the subsequent solution of the sample solution at 405 nm is not more than 0.35 (not more than 400 ppm, as hydrogen peroxide).

(4) Hydrazine – Weigh exactly an amount of Povidone, equivalent to 2.5 g calculated on the anhydrous 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°C 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 0.09 g 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 the Thin-layer Chromatography. Spot 10 μL each of the sample solution and the standard solution on a plate coated with a 0.25 mm layer of dimethylsilanized silica gel with fluorescent indicator for thin-1ayer chromatography. Develop the plate with a mixture of methanol and water (2 : l) 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 *Rf* value of the fluorescent spot from the standard solution is about 0.3, and the fluorescence of the spot from the sample solution corresponding to the spot from the standard solution is not more intense than that of the spot from the standard solution (not more than 1 ppm).

(5) Formic acid – Weigh accurately about 2.0 g of Povidone, dissolve in water to make exactly 100 mL, and use this solution as the sample stock solution. Transfer a suspension of strongly acidic ion exchange resin (H^+ type) for column chromatography in water to a column of about 0.8 cm in inside diameter to give a packing depth of about 20 mm in length, and keep the strongly acidic ion exchange resin layer constantly immersed in water. Pour 5 mL of water, and adjust the flow rate about 1 mL/min. When the level of the water comes down to near the top of the strongly acidic ion exchange resin layer, put the sample stock solution into the column. After dropping 2 mL of the solution, collect 1.5 mL of the solution, and use this solution as the sample solution. Separately, dissolve 0.100 g of formic acid in water to make exactly 100 mL. Pipet 1 mL of this solution and add water to make exactly 100 mL, and use this solution as the standard solution. Perform the test with exactly 50 µL each of the sample solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the peak areas, A_T and A_S, of formic acid in each solution: the content of formic acid is not more than 0.5%

$$\text{Content(\%) of formic acid} = \frac{A_T}{A_S} \times \frac{1.0}{W \times 10}$$

W: Weighed amount (g) of Povidone, calculated on the anhydrous basis.

Operating conditions

Detector: An ultraviolet spectrophotometer (detection wavelength: 210 nm)

Column: Stainless steel columns 7.8 mm in inside diameter and 300 mm in length, packed with strongly acidic ion exchange resin for liquid chromatography (about 10 µm in particle diameter).

Column temperature: A constant temperature of about 35°C

Mobile phase: Diluted perchloric acid (1 in 700).

Flow rate: 1.0 mL/min.

System reproducibility: When the test is repeated six times with the standard solution under the above operating conditions, the relative standard deviation of obtained peak areas of formic acid is not more than 2.0%.

(6) 2-Pyrrolidone – Weigh accurately about 0.5 g of Povidone, dissolve in a mixture

of water and methanol [19:1 (v:v)] 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 [19:1 (v:v)] to make exactly 100 mL. Pipet 2 mL of this solution, add a mixture of water and methanol [19:1 (v:v)] to make exactly 100 mL, and use this solution as the standard solution. Perform the test with exactly 50 µL each of the sample solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the peak areas, A_T and A_S, of 2-pyrrolidone in each solution: the content of 2-pyrrolidone is not more than 3.0%.

$$\text{Content (\%) of 2-pyrrolidone} = \frac{A_T}{A_S} \times \frac{0.3}{W}$$

W: Weighed amount (g) of Povidone, calculated on the anhydrous basis.

Operating conditions –

Detector: An ultraviolet spectrophotometer (detection wavelength: 205 nm)

Column: Stainless steel column 4.0 mm in inside diameter and about 10 mm in length, and 4.6 mm in inside diameter and about 150 mm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 µm in particle diameter), and use them as a guard column and a separation column, respectively.

Column temperature: A constant temperature of about 40°C.

Mobile phase: Water : Methanol [19 : 1 (v : v)]

Flow rate: 0.8 mL/min

System reproducibility: When the test is repeated six times with the standard solution under the above operating conditions, the relative standard deviation of obtained peak areas of 2-pyrrolidone is not more than 2.0%.

Water Not more than 5.0 % (0.5 g) by Karl Fischer method.

Residue on ignition Not more than 0.1 % (1 g).

K-value Weigh accurately an amount of Povidone, calculated on the anhydrous basis, specified in the following table, 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°C as directed in Method 1 under the Viscosity Determination, and calculate the K-value by the following formula. The K-value of Povidone having a nominal K-value of 15 or less is not less than 85.0 % and not more than 115.0 % of the nominal K-value, and the K-value of Povidone having a nominal K-value exceeding 15 is not less than 90.0 % and not more

than 108.0 % 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 Povidone in 100 mL of the solution, calculated on the anhydrous basis.

$v_{rel.}$: Kinematic viscosity of the sample solution relative to that of water.

Nominal K-value	g
18 or less	5.00
more than 18 and not more than 95	1.00
more than 95	0.10

Assay Weight accurately about 0.1 g of Povidone, and place in a Kjeldahl flask. Add 5 g of a powdered mixture of 33 g of potassium sulfate, 1 g of cupric sulfate and 1 g of titanium dioxide, 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 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.

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

REAGENTS

2-Pyrrolidone C_4H_7NO Clear, colorless to pale yellow liquid or white to pale yellow crystalline masses. It is odorless.

Refractive Index n_D^{20}: 1.485~1.490

Congealing Point: 22~26°C

Purity – Weigh accurately about 1.0 g of 2-pyrrolidone, dissolve in methanol to make exactly 10 mL, and use this solution as the sample solution. Perform the test with 1.0 µL of the sample solution as directed under the Gas Chromatography according to the following conditions. Determine each peak area of the solutions by the automatic integration method, and calculate the amount of 2-pyrrolidone by the area percentage method: it is not less than 98.0%.

Operating conditions

Detector: A hydrogen flame-ionization detector.

Column: A hollow, capillary glass column about 0.53 mm in inside diameter and about 30 m in length, having an about 1.0 µm layer of polyethylene glycol 20 M for gas chromatography on the inner side.

Column temperature: Maintain the temperature at 80°C for 1 minute, then raise at the rate of 10°C per minute to 190°C, and hold constant to the temperature for 20 minutes.

Temperature of sample vaporization chamber: A constant temperature of about 200°C. Carrier gas: Helium

Flow rate: Adjust the flow rate so that the retention time of 2-pyrrolidone is about 10 minutes.

Time span of measurement: About twice as long as the retention time of 2-pyrrolidone.

Split ratio: 1.20

Water: Not more than 0.2 %

Acetaldehyde ammonia trimer trihydrate $(C_2H_5N)_3 \cdot 3H_2O$

Purity –Not less than 95.0%