PHARMACOPOEIAL DISCUSSION GROUP
SIGN-OFF DOCUMENT
CODE: E-54
NAME: COPOVIDONE

- Harmonized Attributes

Attribute	EP	JP	USP
Definition	+	+	+
Labelling	+	+	+
Identification*	+	+	+
K-value	+	+	+
pH	+	+	+
Purity			
(1) Clarity and color of solution	+	+	+
(2) Aldehydes	+	+	+
(3) Peroxides	+	+	+
(4) Hydrazine	+	+	+
(5) 1-vinyl-2-pyrorolidone and vinyl acetate	+	+	+
(6) 2-Pyrrolidone	+	+	+
Loss on drying	+	+	+
Residue on ignition	+	+	+
Assay			
Vinyl acetate	+	+	+
Nitrogen	+	+	+

* EP and USP will adopt Copovidone Reference Standard; JP will adopt Reference Spectrum

Legend

+ will adopt and implement; – will not stipulate

Non-harmonized attributes

Characters/Description, Containers and storage/Packaging and storage

Local requirements

EP	JP	USP
Second identification (identifications B, C)	Heavy Metals	Identification B (iodine test)

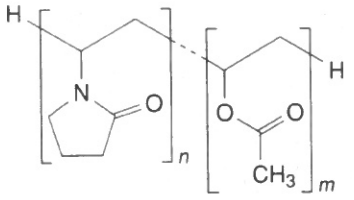
Reagents and reference materials

Each pharmacopoeia will adapt the text to take account of local reference materials and reagent specifications.

Date: 31/01/18 **Signatures:**

European Pharmacopoeia Japanese Pharmacopoeia United States Pharmacopeia

Copovidone



n = 1.16m

$(C_6H_9NO)_n$, $(C_4H_6O_2)_m$ $(C_6H_9NO: 111.14)_n + (C_4H_6O_2: 86.09)_m$

Copolymer of 1-ethenylpyrrolidin-2-one and ethenyl acetate

(Poly[(2-oxopyrrolidin-1-yl)ethylene-co-(1-acetoxyethylene)]) [*25086-89-9*]

Definition

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

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

Labelling

Label it to indicate its nominal K-value.

Identification

Determine the infrared absorption spectrum of Copovidone, previously dried at 105°C for 3 hours, as directed in the potassium bromide disk method under the Infrared Spectrophotometry, and compare the spectrum with the Reference Spectrum or the spectrum of Copovidone Reference Standard previously dried at 105°C for 3 hours: both spectra exhibit similar intensities of absorption at the same wave numbers.

K-value

Weigh exactly an amount of Copovidone, equivalent to 1.000 g, calculated on the dried basis, and 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 Copovidone is not less than 90.0% and not more than 110.0% of the nominal K-value.

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

40

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

pH

Dissolve 1.0 g of Copovidone in 10 ml of water: the pH of this 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 clear or slightly opalescent and colorless to pale yellow or pale red.

(2) Aldehydes - Weigh accurately about 1 g of Copovidone, 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, dissolve 0.140 g of acetaldehyde ammonia trimer trihydrate in water to make exactly 200 mL. Dilute 1.0 mL of this solution, add 0.05 mol/L pyrophosphate buffer solution, pH 9.0 to make exactly 100 mL, and use this solution as the standard solution.
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 those 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 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).

$$\text{Content (ppm) of aldehydes as acetaldehyde} = \frac{(A_{T2} - A_{T1}) - (A_{B2} - A_{B1})}{(A_{S2} - A_{S1}) - (A_{B2} - A_{B1})} \times \frac{C}{M} \times 100000$$

M: Weighed amount (g) of Copovidone, calculated on the dried basis.
C: Concentration (mg/mL) of acetaldehyde in the reference solution, calculated from the weight of the acetaldehyde ammonia trimer trihydrate with the factor 0.72.

(3) 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

4.0

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 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°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-layer chromatography. Develop the plate with a mixture of methanol and water (2:1) to distance of about three-fourths of the length of the plate, and air-dry the plate. Examine under ultraviolet (main wavelength: 365 nm): the R_f value of the fluorescent spot from the standard solution is about 0.3, and the fluorescent of the spot from the sample solution corresponding to the spot from standard solution is not more intense than that of the spot from the standard solution (not more than 1 ppm).

(5) 1-vinyl-2-pyrrolidone and vinyl acetate - Weigh accurately 0.25 g of copovidone and dissolve in a mixture of water and acetonitrile [(23 : 2) (v : v)] to make exactly 10 mL. Use this solution as the sample solution. Separately, transfer 50 mg of each 1-vinyl-2-pyrrolidone and vinyl acetate and dissolve in methanol to make exactly 100 mL. Pipet accurately 1 mL of this solution and add methanol to make exactly 100 mL. Pipet accurately 5 mL of this solution, add a mixture of water and acetonitrile [(23 : 2)(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 Liquid Chromatography according to the following conditions, and determine the peak areas; A_{Ta}, A_{Tb}, A_{Sa}, and A_{Sb} of 1-vinyl-2-pyrrolidone and vinyl acetate in each solution, the content of neither 1-vinyl-2-pyrrolidone nor vinyl acetate is more than 10 ppm. After each injection of the sample solution, elute and wash away the remaining sample by passing the mobile phase through the column backwards for about 30 minutes.

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This process may be replaced by washing the guard column only. Store and inject the solutions at a temperature not exceeding 5°C and use them within 8 hours. Use a cooled autosampler.

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

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

C_{Sa} = concentration of 1-vinyl-2-pyrrolidone in the standard solution (μg/mL) ;

C_{Sb} = concentration of vinyl acetate in the standard solution (μg/mL) ;

C_t = concentration of copovidone in the test solution (mg/mL) ;

Operating conditions -

Detector: An ultraviolet absorption photometer (Wavelength: 235 nm for 1-vinyl-2-pyrrolidone and 205 nm for vinyl acetate)

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

Column temperature: A constant temperature of about 40°C

Mobile phase: A mixture of water and acetonitrile [(23 : 2)(v : v)]

Flow rate: 1.0 ml/min.

Retention time: 1-vinyl-2-pyrrolidone and vinyl acetate are about 17minutes and about 22 minutes.

Time span of measurement: For 40 minutes after injection of the sample solution.

System suitability -

System performance: When the procedure is run with 20 μL of the standard solution at the measuring wavelength of 205 nm under the above operating conditions, 1-vinyl-2-pyrrolidone and vinyl acetate are eluted in this order with the resolution between the 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 deviation of the peak areas of 1-vinyl-2-pyrrolidone and vinyl acetate is not more than 2.0%. Use separate vials for each replicate injection

(6) 2-Pyrrolidone — Weigh accurately about 1 g of Copovidone, and added 5 mL of methanol for liquid chromatography and dissolved by using ultrasonication. Added

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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 (v : v)] to make exactly 100 mL. Pipet 3 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 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 A_S, of 2-pyrrolidone in each solution: the content of 2-pyrrolidone is not more than 0.5%. After each injection of the sample solution, wash away the polymeric material of Copovidone from the column by passing the mobile phase through the column backwards for about 30 minutes at the same flow rate as applied in the test. This process may be replaced by washing the guard column only.

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

C_S = concentration of 2-pyrrolidone in the standard solution (mg/mL) ;

C_t = concentration of copovidone in the test solution (mg/mL) ;

Operating conditions –

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

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 : a mixture of water and methanol [19 : 1 (v : v)]

Flow rate : 0.8 mL/min.

Retention time: 2-pyrrolidone = about 7 min.

Time span of measurement: For 30 minutes after injection of the sample solution.

System suitability -

System performance: When the procedure is run with 20 μL of the standard solution under the above operating conditions, the symmetry factor of the peak of 2-pyrrolidone is not more than 1.5.

System repeatability : When the test is repeated six times with 20 μL of 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%.

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Loss on drying

Not more than 5.0% (0.5 g, 105°C, 3 hours).

Residue on ignition

Not more than 0.1% (1 g).

Assay

Vinyl acetate

Weigh accurately about 2 g of Copovidone into a 250 mL borosilicate glass flask, add an exactly measured 25 mL of 0.5 mol/L potassium hydroxide-ethanol Standard Solution for Volumetric Analysis and a few glass beads, and heat under reflux for 30 min. Titrate immediately (while still hot) with 0.5 mol/L hydrochloric acid Standard Solution for Volumetric Analysis (indicator: 1 mL of phenolphthalein TS)(n_1 mL of 0.5 mol/L hydrochloric acid Standard Solution for Volumetric Analysis). Carry out a blank test under the same conditions (n_2 mL of 0.5 mol/L hydrochloric acid Standard Solution for Volumetric Analysis). Calculate the percentage of copolymerized vinyl acetate in the Copovidone taken by the formula:

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

M: Weighed amount (g) of Copovidone, calculated on the dried basis.

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 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 Standard Solution for Volumetric Analysis 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 Standard Solution for Volumetric Analysis
= 0.700 mg of N