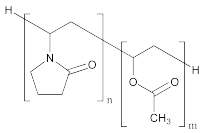
Copovidone



$(C_6H_9NO)_n + (C_4H_6O_2)_m$
Acetic acid ethenyl ester polymer with 1-ethenyl-2-pyrrolidone;
1-Vinyl-2-pyrrolidone polymer with vinyl acetate [25086-89-9].

DEFINITION
Copovidone is a copolymer of 1-vinyl-2-pyrrolidone and vinyl acetate in the mass proportion of 3:2. The nominal K-value of copovidone as stated in the labeling is NLT 90.0% and NMT 110.0%.

IDENTIFICATION
- **A. Infrared Absorption** ⟨197K⟩
- **B.**

Sample solution: 20 mg/mL
Analysis: To 5 mL of the *Sample solution*, add a few drops of iodine TS.
Acceptance criteria: A deep red color is produced.

ASSAY
- **Procedure 1: Content of Copolymerized Vinyl Acetate**

Analysis: Determine the saponification value as directed under *Fats and Fixed Oils* ⟨401⟩, *Saponification Value*. Calculate the percentage of copolymerized vinyl acetate in the portion of Copovidone taken:

$$\text{Result} = 0.1 \times (M_{r1}/M_{r2}) \times S$$

M_{r1} = molecular weight of vinyl acetate, 86.09
M_{r2} = molecular weight of potassium hydroxide, 56.11
S = saponification value

Acceptance criteria: 35.3%–41.4% of the copolymerized vinyl acetate component, calculated on the dried basis

- **Procedure 2: Nitrogen Determination,** *Method II* ⟨461⟩

Analysis: Proceed as directed using 0.1 g of Copovidone. In the procedure, use 5 g of a powdered mixture of potassium sulfate, cupric sulfate, and titanium dioxide (33:1:1) instead of potassium sulfate and cupric sulfate (10:1); omit the use of hydrogen peroxide; and heat until the solution has a clear, yellow-green color and the sides of the flask are free from carbonaceous material. Then heat for a further 45 min; add 20 mL of water, instead of 70 mL, after the second heating; and use bromocresol green–methyl red TS instead of methyl red–methylene blue TS. Titrate the distillate with 0.05 N sulfuric acid VS until the color of the solution changes from green through pale grayish blue to pale grayish red-purple.
Acceptance criteria: 7.0%–8.0% on the dried basis

IMPURITIES
- **Residue on Ignition** ⟨281⟩**:** NMT 0.1%

Add the following:

- **Heavy Metals** ⟨231⟩

Sample solution: 100-mg/mL solution of Copovidone in water. [Note—Add Copovidone to water in small portions with constant stirring.]
Dilute standard lead solution: *Standard Lead Solution* in water (1 in 5)
Standard solution: *Sample solution* and *Dilute standard lead solution* (1:5)
Blank solution: *Sample solution* and water (1:5)
Analysis: To 12 mL each of the *Sample solution*, *Standard solution*, and *Blank solution*, add 2 mL of *pH 3.5 Acetate Buffer*. Mix and add to 1.2 mL of thioacetamide–glycerin base TS. Mix immediately. Examine the solutions after 2 min. [Note—If the result is difficult to judge, filter the solutions through a suitable membrane filter of nominal 0.45-µm pore size. Carry out the filtration slowly and uniformly, applying moderate and constant pressure to the piston. Compare the spots on the filters obtained with the different solutions]
System suitability: The reference solution shows a slight brown color compared to the *Blank solution*.
Acceptance criteria: Any brown color in the *Sample solution* is not more intense than that in the *Standard solution* (NMT 20 ppm). ■2S (NF30)

- **Limit of Aldehydes**

Solution A: 17.4 mg/mL of monobasic potassium phosphate, adjusted if necessary, with 1 N potassium hydroxide to a pH of 9.0
Solution B: Transfer a quantity of lyophilized aldehyde dehydrogenase equivalent to 70 units to a glass vial, and dissolve in 10.0 mL of water. [Note—This solution is stable for 8 h at 4°.]
Solution C: 40 mg of nicotinamide adenine dinucleotide in 10 mL of *Solution A*, in a glass vial. [Note—This solution is stable for 4 weeks at 4°.]
Blank solution: Water
Standard solution: Transfer 2 mL of water at 4° to a glass weighing bottle, and weigh. Add 100 mg of freshly distilled acetaldehyde, and weigh. Transfer this solution to a 100-mL volumetric flask. Rinse the weighing bottle with several portions of water at 4°, and transfer each rinsing to the 100-mL volumetric flask. Dilute the solution in the 100-mL volumetric flask with water at 4° to volume. Store at 4° for 20 h. Transfer 1 mL of this solution to a 100-mL volumetric flask, and dilute with *Solution A* to volume.
Sample solution: 10 mg/mL of Copovidone in *Solution A*, in a 100-mL volumetric flask. Insert a stopper into the flask, heat at 60° for 1 h, and cool to room temperature.
Analysis: Pipet 0.5 mL each of the *Standard solution*, *Sample solution*, and *Blank solution* into separate 1-cm cells. Add 2.5 mL of *Solution A* and 0.2 mL of *Solution C* to each cell. Cover the cells to exclude oxygen. Mix by inversion, and allow to stand for 2–3 min at 22 ± 2°. Determine the absorbances of the solutions at a wavelength of 340 nm. Add 0.05 mL of *Solution B* to each cell. Cover the cells to exclude oxygen. Mix by inversion, and allow to stand for 5 min at 22 ± 2°. Determine the absorbances of the solutions at a wavelength of 340 nm.
Calculate the percentage of aldehydes, expressed as acetaldehyde, in the portion of Copovidone taken:

$$\text{Result} = \{[(A_{U2} - A_{U1}) - (A_{B2} - A_{B1})]/[(A_{S2} - A_{S1}) - (A_{B2} - A_{B1})]\} \times (C/W) \times 10$$

A_{U2} = absorbance of the solution from the *Sample solution*, after the addition of *Solution B*
A_{U1} = absorbance of the solution from the *Sample solution*, before the addition of *Solution B*
A_{B2} = absorbance of the solution from the *Blank solution*, after the addition of *Solution B*
A_{B1} = absorbance of the solution from the *Blank solution*, before the addition of *Solution B*
A_{S2} = absorbance of the solution from the *Standard solution*, after the addition of *Solution B*
A_{S1} = absorbance of the solution from the *Standard solution*, before the addition of *Solution B*
C = concentration of acetaldehyde in the *Standard solution* (mg/mL)

W = weight, calculated on the dried basis, of Copovidone taken to prepare the *Sample solution* (g)

Acceptance criteria: NMT 0.05%

- **LIMIT OF HYDRAZINE**

Standard solution: 9 µg/mL of salicylaldazine and 10 mg/mL of salicylaldehyde in toluene

Sample solution: Transfer the equivalent of 2.5 g of dried Copovidone to a 50-mL centrifuge tube, add 25 mL of water, and mix to dissolve. Add 500 µL of a 50-mg/mL solution of salicylaldehyde in methanol, adjust the solution with 0.25 N sulfuric acid to a pH of about 2, swirl, and heat in a water bath at 60° for 15 min. Allow to cool, add 2.0 mL of toluene, insert a stopper in the tube, shake vigorously for 2 min, and centrifuge. Use the clear upper toluene layer.

Chromatographic system

(See *Chromatography* ⟨621⟩*, Thin-Layer Chromatography*.)

Adsorbent: 0.25-mm layer of dimethylsilanized chromatographic silica gel mixture

Application volume: 10 µL

Developing solvent system: Acetonitrile and water (17:3)

Analysis

Samples: *Standard solution* and *Sample solution*

Proceed as directed in the chapter. Allow the spots to dry, and develop the chromatogram in the *Developing solvent system* until the solvent front has moved about three-fourths of the length of the plate. Locate the spots on the plate by examination under UV light at a wavelength of 365 nm: salicylaldazine appears as a fluorescent spot having an R_F value of about 0.6–0.7, and the fluorescence of any salicylaldazine spot from the *Sample solution* is not more intense than that produced by the spot from the *Standard solution*.

Acceptance criteria: NMT 1 ppm

- **LIMIT OF PEROXIDES**

Copovidone solution: 40 mg/mL of Copovidone in water calculated on the dried basis

Sample solution: Transfer 25.0 mL of *Copovidone solution* to a 50-mL beaker, and add 2 mL of titanium trichloride–sulfuric acid TS. Allow to stand for 30 min at room temperature.

Blank solution: Transfer 25.0 mL of *Copovidone solution* to a 50-mL beaker, and add 2 mL of 13% sulfuric acid.

Spectrometric conditions

(See *Spectrophotometry and Light-Scattering* ⟨851⟩.)

Mode: UV-Vis

Analytical wavelength: 405 nm

Cell: 1 cm

Blank: *Blank solution*

Analysis: Determine the absorbance of the *Sample solution*.

Acceptance criteria: The absorbance is NMT 0.35 (corresponding to NMT 0.04%, expressed as hydrogen peroxide).

Delete the following:

- **PROCEDURE 4: LIMIT OF MONOMERS**

Sample solution: Dissolve the equivalent of 5.0 g of dried Copovidone in 20 mL of methanol, and slowly add 20.0 mL of iodobromide TS. Allow to stand for 30 min, protected from light, with repeated shaking. Add 5 mL of 100 mg/mL of potassium iodide solution.

Analysis: Titrate the liberated iodine with 0.1 N sodium thiosulfate VS until the solution is yellow. Continue the titration dropwise until the solution is colorless, adding 3 mL of starch TS as the endpoint is approached. Perform a blank determination (see *Titrimetry* ⟨541⟩*, Residual Titrations*).

Acceptance criteria: The difference between the volumes of 0.1 N sodium thiosulfate consumed in the blank and the specimen titrations is NMT 0.9 mL, corresponding to NMT 0.1% of monomers calculated as vinylpyrrolidone. ■2S (NF30)

Add the following:

- **LIMIT OF MONOMERS (1-VINYL-2-PYRROLIDONE, VINYL ACETATE, AND 2-PYRROLIDONE)**

Solution A: Water, acetonitrile, and methanol (90:5:5)

Solution B: Water, acetonitrile, and methanol (50:45:5)

Mobile phase: See *Table 1*.

Table 1

Time (min)	Solution A (%)	Solution B (%)
0	100	0
2	100	0
26	80	20
27	0	100
36	0	100
38	100	0

Standard stock solution: 0.50 mg/mL of 1-vinyl-2-pyrrolidone, 0.50 mg/mL of vinyl acetate, and 3.0 mg/mL of 2-pyrrolidone in methanol

Standard solution: *Standard stock solution* in *Solution A* (1 in 2000)

Sample solution: Dissolve 250 mg of Copovidone in 1 mL of methanol, mix ultrasonically, dilute with water to 10 mL. If necessary, filter to remove undissolved particles.

Chromatographic system

(See *Chromatography* ⟨621⟩*, System Suitability*.)

Mode: LC

Detector: UV 205 nm and 235 nm

Column

Guard: 4.0-mm × 2.5-cm; packing L1

Analytical: 4.0-mm × 25-cm; 5-µm packing L1

Column temperature: 30°

Injection size: 10 µL

Flow rate: 1.0 mL/min

System suitability

Sample: *Standard solution*

Suitability requirements

Resolution: NLT 2.0 between the 2-pyrrolidone and vinyl acetate peaks, and NLT 2.0 between the vinyl acetate and 1-vinyl-2-pyrrolidone peaks. [NOTE—According to the above operating conditions, the order of elution is 2-pyrrolidone, vinyl acetate, and 1-vinyl-2-pyrrolidone.]

Relative standard deviation: NMT 2.0% for each analyte, on replicate injections

Analysis

Samples: *Standard solution* and *Sample solution*

[NOTE—After each injection of the *Sample solution* wash the polymeric material of Copovidone from the guard column by passing the *Mobile phase* through the column backwards for 30 min at the same flow rate.]

Calculate the content of 1-vinyl-2-pyrrolidone in the portion of Copovidone taken:

$$\text{Result} = (A_{TA}/A_{SA}) \times (C_{SA}/C_T) \times 100$$

A_{TA} = 1-vinyl-2-pyrrolidone peak response from the *Sample solution*

A_{SA} = 1-vinyl-2-pyrrolidone peak response from the *Standard solution*

C_{SA} = concentration of 1-vinyl-2-pyrrolidone in the *Standard solution* (mg/mL)

C_T = concentration of Copovidone in the *Sample solution* on the dried basis (mg/mL)

Calculate the content of vinyl acetate in the portion of Copovidone taken:

$$\text{Result} = (A_{TB}/A_{SB}) \times (C_{SB}/C_T) \times 100$$

A_{TB} = vinyl acetate peak response from the *Sample solution*
A_{SB} = vinyl acetate peak response from the *Standard solution*
C_{SB} = concentration of vinyl acetate in the *Standard solution* (mg/mL)
C_T = concentration of Copovidone in the *Sample solution* on the dried basis (mg/mL)

Calculate the content of 2-pyrrolidinone in the portion of Copovidone taken:

$$\text{Result} = (A_{TC}/A_{SC}) \times (C_{SC}/C_T) \times 100$$

A_{TC} = 2-pyrrolidone peak response from the *Sample solution*
A_{SC} = 2-pyrrolidone peak response from the *Standard solution*
C_{SC} = concentration of 2-pyrrolidone in the *Standard solution* (mg/mL)
C_T = concentration of Copovidone in the *Sample solution* on the dried basis (mg/mL)

Acceptance criteria: NMT 0.001% of 1-vinyl-2-pyrrolidone, NMT 0.001% of vinyl acetate, and NMT 0.5% of 2-pyrrolidone ■2S (NF30)

SPECIFIC TESTS

- **Loss on Drying ⟨731⟩:** Dry a sample at 105° for 3 h: it loses NMT 5.0% of its weight.
- **Clarity and Color of Solution**
  Sample: 1.0 g
  Analysis: Dissolve the *Sample* in 10 mL of water.
  Acceptance criteria: The solution is clear or slightly opalescent and colorless to pale yellow or pale red.
- **K-Value**
  Sample solution: Transfer a quantity of undried Copovidone, equivalent to 1.0 g on the dried basis, to a 100-mL volumetric flask, and dissolve in and dilute with water to volume. Allow to stand for 1 h.
  Analysis: Determine the viscosity, using a capillary-tube viscometer (see *Viscosity—Capillary Viscometer Methods* ⟨911⟩), of this solution at 25 ± 0.2°.
  Calculate the relative K-value of Copovidone:

$$\text{Result} = \left[\sqrt{300c\log z + (c + 1.5c\log z)^2} + 1.5c\log z - c\right] \Big/ \left(0.15c + 0.003c^2\right) \times (100/K_U)$$

c = weight on the dried basis, of the specimen tested in each 100.0 mL of solution (g)
z = viscosity of the *Sample solution* relative to that of water
K_U = nominal K-value stated on the label

Acceptance criteria: 90.0%–110.0%

ADDITIONAL REQUIREMENTS

- **Packaging and Storage:** Preserve in tight containers. No storage requirements specified.
- **Labeling:** Label it to indicate its nominal K-value.
- **USP Reference Standards ⟨11⟩**
  USP Copovidone RS

Add the following:

■Ferrosoferric Oxide

Fe_3O_4 ($FeO \cdot Fe_2O_3$) 231.54
Magnetite;
Ferrous-ferric oxide;
Iron (II, III) oxide [1317-61-9].

DEFINITION

Ferrosoferric Oxide contains NLT 97.0% and NMT 100.5% of Fe_2O_3, calculated on the ignited basis.

IDENTIFICATION

- **A.**
  Sample solution: Dissolve 0.1 g in 5 mL of hydrochloric acid, and dilute with water to 50 mL.
  Analysis 1: Transfer 5 mL of the *Sample solution* to a test tube, and add a few drops of potassium ferrocyanide TS.
  Analysis 2: Transfer 5 mL of the *Sample solution* to a test tube, and add a few drops of potassium ferricyanide TS.
  Acceptance criteria: For both *Analysis 1* and *Analysis 2*, a blue precipitate (Prussian blue) is formed, which does not dissolve in dilute hydrochloric acid subsequently added. The precipitate dissolves in oxalic acid and sodium or potassium hydroxide.
- **B.** Ferrosoferric Oxide presents as black powder, which is distinguished from ferric oxide exhibiting two basic colors (red and yellow). It is attracted to a magnet.

ASSAY

- **Procedure**
  To enable the calculation of the percentage of Fe_2O_3 on the ignited basis, ignite about 2 g at 800 ± 25° to constant weight as directed in *Loss on Ignition* ⟨733⟩.
  [Note—Ignited Ferrosoferric Oxide is hygroscopic.]
  Sample: 1.5 g
  Blank: 25 mL of hydrochloric acid
  Titrimetric system
  (See *Titrimetry* ⟨541⟩.)
  Mode: Direct titration
  Titrant: 0.1 N sodium thiosulfate VS
  Endpoint detection: Visual
  Analysis: Digest the *Sample* in 25 mL of hydrochloric acid on a water bath until dissolved. Add 10 mL of hydrogen peroxide TS, and evaporate on a water bath almost to dryness in order to volatilize all hydrogen peroxide. Dissolve the residue by warming with 5 mL of hydrochloric acid; add 25 mL of water; filter into a 250-mL volumetric flask, washing the filter with water; and add water to volume. Transfer a 50-mL aliquot to a glass-stoppered flask, add 3 g of potassium iodide and 5 mL of hydrochloric acid, and insert the stopper into the flask. Allow the mixture to stand for 15 min, add 50 mL of water, and titrate the liberated iodine with 0.1 N sodium thiosulfate VS, using starch TS as the indicator. Perform a blank determination in the same manner.
  Calculate the percentage of the labeled amount as ferric oxide (Fe_2O_3) in the portion of the *Sample* taken:

$$\text{Result} = \{[(V_S - V_B) \times N \times F]/W\} \times 100$$

V_S = *Titrant* volume consumed by the *Sample* (mL)
V_B = *Titrant* volume consumed by the *Blank* (mL)
N = actual normality of the *Titrant* (mEq/mL)
F = equivalency factor, 79.85 mg/mEq
W = weight of the *Sample*, calculated with a correction for loss on ignition (mg)

Acceptance criteria: 97.0%–100.5% on the ignited basis

IMPURITIES

- **Limit of Arsenic (As)**
  [Note—Select all reagents to have as low contents of heavy metals as practicable, and store all reagent