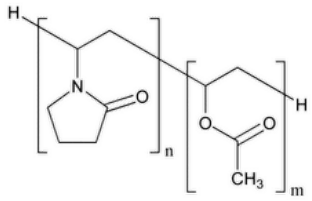
Status: Currently Official on 14-Feb-2025
Official Date: Official as of 01-May-2021
Document Type: NF Monographs
DocId: GUID-D8A5F0D7-9622-47C3-B23A-4AA38DC95547_6_en-US
DOI: https://doi.org/10.31003/USPNF_M20030_06_01
DOI Ref: 4gvw6

Copovidone

Add the following:

▲Portions of this monograph that are national *USP* text, and are not part of the harmonized text, are marked with symbols (◆) to specify this fact.▲ (NF 1-May-2021)

Change to read:



$(C_6H_9NO)_n$ + $(C_4H_6O_2)_m$ ▲(n = 1.16m)▲ (NF 1-May-2021)
Acetic acid ethenyl ester polymer with 1-ethenyl-2-pyrrolidone;
1-Vinyl-2-pyrrolidone polymer with vinyl acetate;
▲(Poly[(2-oxopyrrolidin-1-yl)ethylene-co-(1-acetoxyethylene)]);
Copolymer of 1-ethenylpyrrolidin-2-one and ethenyl acetate▲ (NF 1-May-2021)

CAS RN®: 25086-89-9.

DEFINITION

Change to read:

Copovidone is a copolymer of 1-vinyl-2-pyrrolidone and vinyl acetate in the mass proportion of 3:2. ▲It contains NLT 7.0% and NMT 8.0% of nitrogen (N: 14.01), and NLT 35.3% and NMT 42.0% of vinyl acetate ($C_4H_6O_2$: 86.09), calculated on the dried basis.▲ (NF 1-May-2021)

IDENTIFICATION

Change to read:

• **A. Spectroscopic Identification Tests ⟨197⟩, *Infrared Spectroscopy*: 197K**

▲Sample: Dry at 105° for 3 h.

Acceptance criteria: Meets the requirements▲ (NF 1-May-2021)

Change to read:

• **▲◆▲** (NF 1-May-2021) **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.**▲◆▲** (NF 1-May-2021)

ASSAY

Change to read:

• **Procedure 1: Content of Copolymerized Vinyl Acetate**

▲Sample: 2 g of Copovidone▲ (NF 1-May-2021)

Analysis: Determine the saponification value as directed under *Fats and Fixed Oils ⟨401⟩, Procedures, 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%–▲42.0%▲ (NF 1-May-2021) of the copolymerized vinyl acetate component, calculated on the dried basis

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

Sample: 0.1 g of Copovidone

Analysis: Proceed as directed using the *Sample*. 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% of Nitrogen on the dried basis

IMPURITIES

Change to read:

• **Residue on Ignition ⟨281⟩**

▲**Sample:** 1 g of Copovidone▲ (NF 1-May-2021)

Acceptance criteria: NMT 0.1%

Change to read:

• **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 β-nicotinamide adenine dinucleotide in 10 mL of *Solution A*, in a glass vial. [Note—This solution is stable for 4 weeks at 4°.]

▲▲ (NF 1-May-2021)

Standard solution: ▲Transfer an equivalent to about 0.140 g of acetaldehyde ammonia trimer trihydrate and dissolve it in water to make exactly 200 mL.▲ (NF 1-May-2021) Transfer 1 mL of this solution to a 100-mL volumetric flask, and dilute with *Solution A* to volume.

Sample solution: ▲Transfer an equivalent to about 1 g of Copovidone and dissolve it▲ (NF 1-May-2021) in *Solution A*▲to exactly 100 mL in a▲ (NF 1-May-2021) 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 ▲water (used for the blank test)▲ (NF 1-May-2021) into separate 1-cm cells. Add 2.5 mL of *Solution A* and 0.2 mL of *Solution C* to each cell. ▲◆▲ (NF 1-May-2021) Cover the cells to exclude oxygen.▲◆▲ (NF 1-May-2021) 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, ▲using water as a reference.▲ (NF 1-May-2021) 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, ▲using water as a reference.▲ (NF 1-May-2021)

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,▲ (NF 1-May-2021) after the addition of *Solution B*

A_{B1} = absorbance of the solution from the ▲blank,▲ (NF 1-May-2021) 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), ▲calculated from the weight of the acetaldehyde ammonia trimer trihydrate with a factor of 0.72. ◆

[NOTE—The molar mass of acetaldehyde is 44.05 g/mol, and the molar mass of acetaldehyde ammonia trimer trihydrate is 183.26 g/mol. (44.05 × 3)/183.26 = 0.72]

◆▲ (NF 1-May-2021)

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

Acceptance criteria: NMT 0.05% ▲(500 ppm)▲ (NF 1-May-2021)

Change to read:

• **LIMIT OF HYDRAZINE**

Standard solution: 9 µg/mL of salicylaldazine ▲▲ (NF 1-May-2021) 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, ▲stir,▲ (NF 1-May-2021) 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 ▲tightly,▲ (NF 1-May-2021) shake vigorously for 2 min, and centrifuge. Use the clear upper toluene layer.

Chromatographic system

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

Adsorbent: 0.25-mm layer of dimethylsilanized chromatographic silica gel ▲with a fluorescent indicator▲ (NF 1-May-2021)

Application volume: 10 µL

Developing solvent system: ▲Methanol and water (2:1)

Analytical wavelength: UV 365 nm▲ (NF 1-May-2021)

Analysis

Samples: *Standard solution* and *Sample solution*

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. Salicylaldazine appears as a fluorescent spot having an R_F value of about ▲0.3,▲ (NF 1-May-2021) 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

Change to read:

• **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.

Instrumental conditions

(See *Ultraviolet-Visible Spectroscopy ⟨857⟩*.)

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% ▲(400 ppm),▲ (NF 1-May-2021) expressed as hydrogen peroxide].

Delete 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

Columns

Guard: 4.0-mm × 2.5-cm; packing L1

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

Column temperature: 30°

Injection volume: 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-pyrrolidone 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▲ (NF 1-May-2021)

Change to read:

- **▲Limit of Monomers (1-Vinyl-2-Pyrrolidone and Vinyl Acetate)**

Mobile phase: Water and acetonitrile (23:2)

Standard stock solution: 5 µg/mL of 1-vinyl-2-pyrrolidone and 5 µg/mL of vinyl acetate in methanol

Standard solution: 0.25 µg/mL of 1-vinyl-2-pyrrolidone and ▲0.25▲ (ERR 1-May-2021) µg/mL of vinyl acetate, respectively, diluted from the *Standard stock solution* in *Mobile phase*

Sample solution: 25 mg/mL of Copovidone in *Mobile phase*

[Note—Store the *Sample solution* and both *Standard solution* at a temperature NMT 10°, and use within 8 h.]

Chromatographic system

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

Mode: LC

Detector: UV 235 nm for 1-vinyl-2-pyrrolidone; UV 205 nm for vinyl acetate

Columns

Guard: 4.0-mm × 33-mm; 5-µm packing L1

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

Column temperature: 40°

Flow rate: 1.0 mL/min

Injection volume: 20 µL

Run time: 40 min

System suitability

Sample: *Standard solution*

[Note—The retention times for 1-vinyl-2-pyrrolidone and vinyl acetate are about 17 and 22 min, respectively.]

Suitability requirements

Resolution: NLT 2.0 between 1-vinyl-2-pyrrolidone and vinyl acetate, at the measuring wavelength of 205 nm

Relative standard deviation: NMT 2.0% for each analyte, on 6 replicate injections of the *Standard solution*

Analysis

Samples: *Standard solution* and *Sample solution*

[Note—After each test with the *Sample solution,* wash the polymeric material of Copovidone from the column by passing the *Mobile phase* through the column backwards for about 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} = peak response of 1-vinyl-2-pyrrolidone from the *Sample solution*

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

A_{SB} = peak response of vinyl acetate 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)

Acceptance criteria

1-Vinyl-2-pyrrolidone: NMT 0.001% (10 ppm)

Vinyl acetate: NMT 0.001% (10 ppm)▲ (NF 1-May-2021)

Add the following:

▲• **Limit of 2-Pyrrolidone**

Mobile phase: Water and methanol (19:1)

Standard solution: 45 µg/mL of 2-pyrrolidone in *Mobile phase*

Sample solution: Accurately weigh about 1 g of Copovidone, transfer to a 100-mL volumetric flask, add 5 mL of methanol, and dissolve by using ultrasonication. Dilute with water to 100 mL.

Chromatographic system

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

Mode: LC

Detector: UV 205 nm

Columns

Guard: 4.0-mm × 10-mm; 5-µm packing L1

Analytical: 4.6-mm × 15-cm; 5-µm packing L1

Column temperature: 40°

Flow rate: 0.8 mL/min

Injection volume: 20 µL

Run time: 30 min

System suitability

Sample: *Standard solution*

[NOTE—The retention time for 2-pyrrolidone is about 7 min.]

Suitability requirements

Column efficiency: NLT 5000 theoretical plates for the 2-pyrrolidone peak

Symmetry factor: NMT 1.5 for the 2-pyrrolidone peak

Relative standard deviation: NMT 2.0% for 6 replicate injections of *Standard solution*

Analysis

Samples: *Standard solution* and *Sample solution*

[NOTE—After each test with the *Sample solution*, wash the polymeric material of Copovidone from the column by passing the *Mobile phase* through the column backward for about 30 min at the same flow rate.]

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

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

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

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

C_{SA} = 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 0.5% ▲(NF 1-May-2021)

SPECIFIC TESTS

Add the following:

▲• **pH** ⟨791⟩

Sample solution: 100 mg/mL of Copovidone in water

Acceptance criteria: 3.0–7.0 ▲(NF 1-May-2021)

Change to read:

• **Loss on Drying** ⟨731⟩

▲**Sample:** 0.5 g of Copovidone ▲(NF 1-May-2021)

Analysis: Dry a sample at 105° for 3 h.

Acceptance criteria: NMT 5.0%

• **Clarity and Color of Solution**

Sample: 1.0 g of Copovidone

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.

Change to read:

• **K-Value**

Sample solution: ▲Transfer an amount ▲(NF 1-May-2021) of undried Copovidone, equivalent to ▲1.00 ▲(NF 1-May-2021) g on the dried basis, ▲and transfer ▲(NF 1-May-2021) 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 Methods* ⟨911⟩), of this solution at 25 ± 0.2°. Calculate the relative K-value of Copovidone:

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

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% ▲of the nominal K-value stated on the label of the vial as required by the *Labeling* section ▲(NF 1-May-2021)

ADDITIONAL REQUIREMENTS

Change to read:

• ▲◆▲(NF 1-May-2021) **Packaging and Storage:** Preserve in tight containers. No storage requirements specified. ▲◆▲(NF 1-May-2021)

• **Labeling:** Label it to indicate its nominal K-value.

• **USP Reference Standards** ⟨11⟩

USP Copovidone RS

Auxiliary Information - Please check for your question in the FAQs before contacting USP.

Topic/Question	Contact	Expert Committee
COPOVIDONE	Documentary Standards Support	CE2020 Complex Excipients

Chromatographic Database Information: Chromatographic Database

Most Recently Appeared In:
Pharmacopeial Forum: Volume No. PF 42(3)

Current DocID: GUID-D8A5F0D7-9622-47C3-B23A-4AA38DC95547_6_en-US

DOI: https://doi.org/10.31003/USPNF_M20030_06_01

DOI ref: 4gvw6