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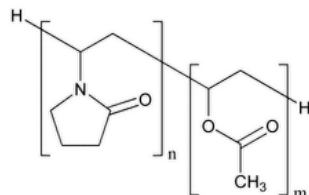
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Copovidone

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. $(44.05 \times 3)/183.26 = 0.72$]

▲ (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)