Copovidone

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Manufacturers, regulatory authorities, health authorities, researchers, and other stakeholders are invited to provide their feedback and comments on this draft proposal. Manufacturers are also invited to submit samples of their products to the IPC to ensure that the proposed monograph adequately controls the quality of the product(s) they manufacture. Comments and samples received after the last date will not be considered by the IPC before finalizing the monograph.

Please send any comments you may have on this draft document to lab.ipc@gov.in, with a copy to Dr. Gaurav Pratap Singh (email: gpsingh.ipc@gov.in) before the last date for comments.

Document History and Schedule for the Adoption Process

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Copovidone

Copovidone is 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.
$(C_6H_9NO)n + (C_4H_6O_2)m$ (n = 1.16m)

Portions of the monograph text that are IP *text, and are not part of the PDG harmonized text, are marked with symbols (‧‧)*

Copovidone is a copolymer of 1-vinyl-2-pyrrolidone and vinylacetate in the mass proportion of 3:2. Copovidone contains not less than 7.0 per cent and not more than 8.0 per cent of nitrogen (N:14.01), and not less than 35.3 per cent and not more than 42.0 per cent of vinyl acetate ($C_4H_6O_2$: 86.09), calculated on the dried basis.

It contains not less than 90.0 per cent and not more than 110.0 per cent of the nominal K-value stated on the label.
Category. Pharmaceutical aid.

Description. A white to yellowish-white powder or flakes.

Identification

A. Determine by infrared absorption spectrophotometry (2.4.6) on specimen (previously dried at 105° for 3 hours). Compare the spectrum with that obtained with *copovidone IPRS,* or with the reference spectrum of copovidone.

B. Dissolve 0.5 g in 25 ml of *wate*r. To 5.0 ml of this solution, add a few drops of *iodine*; a deep red colour is produced.

Tests

Appearance of solution. A 10.0 per cent w/v solution in *water* is clear (2.4.1) and not more intensely coloured than reference solution BSY_5 (2.4.1).

pH (2.4.24). 3.0 to 7.0, determined in 10.0 per cent w/v solution.

Limit of Aldehydes. Not more than 0.05 per cent,

Solution A. Dissolve 17.4 g of *potassium dihydrogen orthophosphate* in 1000 ml of *water*, adjusted to pH 9.0 with *1M potassium hydroxide*.

Solution B. Transfer a quantity of *lyophilized aldehyde hydrogenase* equivalent to70 units to a glass vial, and dissolve in 10.0 ml of *water*. [*NOTE—This solution is stable for 8 hours at 4˚*].

Solution C. Dissolve 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*°.]

Test solution. Dissolve an equivalent to about 1 g of Copovidone in solution A and dilute to 100.0 ml with solution A. Insert stopper into the flask, heat at 60° for 1 hour, and cool to room temperature.

Reference solution. Dissolve equivalent to about 0.14 g of *acetaldehyde ammonia trimer trihydrate* in *water* and dilute to 200.0 ml with *water*. Dilute 1.0 ml of the solution to a 100.0 ml with solution A.

Pipet 0.5 ml, each of the reference solution, test solution, and water (used for the blank test) 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 minutes at 22 ± 2°. Measure the absorbances of the solutions at the maximum at about 340 nm (2.4.7), using

water as a reference. 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 minutes at 22 ± 2°. Measure the absorbances of the solutions at the maximum at about 340 nm, using water as a reference.

Calculated the percentage of aldehyde, in the portion of copovidone using following expression:

$$\text{Result} = \frac{[(AU_2 - AU_1) - (AB_2 - AB_1)]}{[(AS_2 - AS_1) - (AB_2 - AB_1)]} \times \frac{C}{W} \times 10$$

where,
AU_2,= absorbance of the solution from the test solution, after the addition of solution B,
AU_1,= absorbance of the solution from the test solution, before the addition of solution B,
AB_2 = absorbance of the solution from the blank, after the addition of solution B,
AB_1 = absorbance of the solution from the blank, before the addition of solution B,
AS_2 = absorbance of the solution from the reference solution, after the addition of solution B,
AS_1 = absorbance of the solution from the reference solution, before the addition of solution B,
C = concentration of aldehyde in the reference solution (mg/ml), calculated from the weight of the acetaldehyde ammonia trimer trihydrate with a factor of 0.72.
W = Weight, calculated on the dried basis of copovidone used to prepare test solution (g).

Limit of Hydrazine. Not more than 1 ppm, determined by thin-layer chromatography (2.4.17), coating the plate with dimethylsilanized silica gel GF 254.

Mobile phase. A mixture of 66.5 volumes of *methanol* and 33.5 volumes of *water*.

Test solution. Dissolve an equivalent of 2.5 g of dried Copovidone in 25.0 ml of *water* in a 50-ml centrifuge tube, add 500 µl of a 5.0 per cent w/v solution of *salicylaldehyde* in *methanol*, stir and heat in a water bath at 60˚ for 15 minutes. Allow to cool, add 2.0 ml of *toluene,* insert a stopper in the tube tightly, shake vigorously for 2 minutes and centrifuge. Use the clear upper toluene layer.

Reference solution. A 0.0009 per cent w/v solution of *salicylaldazine* in *toluene*.

Apply to the plate 10 µl of each solution, allow the mobile phase to rise three-fourth of the length of the plate. Dry the plate in air and examine under UV light at 365 nm. Any spot having Rf value of about 0.3 in the chromatogram obtained with the test solution is not more intense than the spot in the chromatogram obtained with the reference solution.

Limit of peroxides. The absorbance is not more than 0.35 (corresponding to not more than 0.04 per cent, expressed as hydrogen peroxide).

Copovidone solution. Dissolve 4 g of Copovidone (calculated on dried basis) in *water* and dilute to 100.0 ml with *water*.

Test solution. Transfer 25.0 ml of Copovidone solution to a 50-ml beaker, and add 2.0 ml of *titanium trichloride- sulphuric acid solution*. Allow to stand for 30 minutes at room temperature.

Blank solution. Transfer 25.0 ml of Copovidone solution to a 50-ml beaker, and add 2.0 ml of 13 per cent v/v of *sulphuric acid*.

Measure the absorbance of the resulting solution at the maximum at about 405 nm (2.4.7).

Limit of monomers (1-vinyl-2-pyrrolidone and vinyl acetate). Not more than 0.001 per cent; 1-vinyl-2-pyrrolidone, and not more than 0.001 per cent of vinyl acetate. Determine by liquid chromatography (2.4.14).

[*NOTE—Store the solutions at a temperature not exceeding 10˚*].

Test solution. Dissolve 0.5 g of substance under examination in the mobile phase and dilute to 20.0 ml with the mobile phase.

Reference solution. A solution containing 0.0005 per cent w/v, each of, *1-vinyl-2-pyrrolidone* and *vinyl acetate* in *methanol*. Dilute 1.0 ml of the solution in 20.0 ml with the mobile phase.

Chromatographic system

- a stainless steel column 25 cm x 4.0 mm, packed with octadecylsilane bonded to porous silica (5 µm) and a guard column 3.3 cm x 4.0 mm packed with the octadecylsilane bonded to porous silica (5 µm),
- column temperature: 40˚,
- mobile phase: a mixture of 92 volumes of *water*, and 8 volumes of *acetonitrile*.
- flow rate:1 ml per minute,
- spectrophotometer set at 235 nm for 1-vinyl-2-pyrrolidone and 205 nm for vinyl acetate,
- injection volume: 20 µl,

The retention times for 1-vinyl-2-pyyrrolidone and vinylacetate are about 17 and 22 minutes, respectively.

Inject the reference solution at 205 nm. The test is not valid unless the resolution between the peaks due to 1-vinyl-2-pyrrolidone and vinyl acetate is not less than 2.0 and the relative standard deviation for replicate injections is not more than 2.0 per cent, for both the peaks.

Inject the reference solution and the test solution at 205 nm.

Calculate the content of vinyl acetate.

Inject the reference solution and the test solution at 235 nm.

Calculate the content of 1-vinyl-2-pyrrolidone.

NOTE- After each test with the test solution, wash the polymeric material of copovidone from the column by passing the mobile phase through the column back ward for about 30 minutes at the same flow rate.

Limit of 2-pyrrolidone. Not more than 0.5 per cent.

Determine by liquid chromatography (2.4.14).

Test solution. Dissolve 1 g of the substance under examination in 5 ml of *methanol*, with the aid of ultrasound and dilute to 100.0 ml with *water*.

Reference solution. A 0.0045 per cent w/v solution of *2-pyrrolidone* in the mobile phase,

Chromatographic system

- a stainless steel column 15 cm x 4.6 mm, packed with octadecylsilane bonded to porous silica (5 µm) and a guard column 10 cm x 4.0 mm packed with octadecylsilane bonded to porous silica (5 µm),
- column temperature: 40º,
- mobile phase: a mixture of 95 volumes of *water* and 5 volumes of *methanol*.
- flow rate: 0.8 ml per minute,
- spectrophotometer set at 205 nm,
- injection volume: 20 µl.

The retention time of 2-pyrrolidone is about 7 minutes.

Inject the reference solution. The test is not valid unless the column efficiency is not less than 5000 theoretical plates, the tailing factor is not more than 1.5 and the relative standard deviation for replicate injections is not more than 2.0 per cent.

Inject the reference solution and the test solution.

Calculate the content of 2-pyrrolidone.

K –Values. Not less than 90.0 per cent and not more than 110.0 per cent of the nominal K-value stated on the label.
Test solution. Dissolve a quantity of undried substance under examination equivalent to 1.0 g dried substance in *water* and dilute to100.0 ml with *water*. Allow to stand for 1 hour.

Determine the viscosity (2.4.28), using a capillary-tube viscometer at 25º and calculate the relative K-value of Copovidone by using following expression;

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

C = weight on the dried basis, of the specimen tested in each 100.0 ml of solution (g).
z= viscosity of the test solution relative to that of water.
K_u = Nominal K-Value stated on the label.

Heavy metals (2.3.13). 1.0 g complies with the limit test for heavy metals, Method B (20 ppm).

Sulphated ash (2.3.18). Not more than 0.1 per cent.

Loss on drying (2.4.19). Not more than 5.0 per cent, determined on 0.5 g by drying in an oven at 105˚ for 3 hours.

Assay.

A. Content of Copolymerized Vinyl acetate. Not less than 35.3 per cent and not more than 42.0 per cent, calculated on the dried basis.

Determined the saponification value (2.3.37) on 2 g of copovidone and calculate the percentage of copolymerized vinyl acetate in the portion of copovidone, using following expression;

Result = $0.1 \times (Mr_1/Mr_2) \times S$
Mr_1 = molecular weight of vinyl acetate, 86.09.
Mr_2 = molecular weight of potassium hydroxide, 56.11.
S = saponification value

B. Nitrogen (2.3.30). Not less than 7.0 per cent and not more than 8.0 per cent, calculated on the dried basis. Determine by Method C.

Procedure. Place 0.1 g of the substance under examination in a combustion flask, add 5 g of a powdered mixture of 1 g of *cupric sulphate*,1 g of *titanium dioxide* and 33 g of *potassium sulphate* instead of 10 parts of *anhydrous sodium sulphate* or *potassium sulphat*e and 1 part of *cupric sulphate*; omit the use of *hydrogen peroxide*; heat until the solution has a clear, yellow- green colour and the sides of the flask are free from carbonaceous material. Continue the heating for 45 minutes. Cool, and add 20 ml of *water* and place in a steam-distillation apparatus. Towards the end of the distillation lower the receiver so that the tip of the condenser is above the surface of the acid solution and rinse the end part of the condenser with a small quantity of water. Titrate the distillate with *0.05 M sulphuric acid* using bromocresol green-methyl red as indicator, until the colour of the solution changes from green through pale greyish-blue to pale greyish-red- purple.

Storage. Store protected from moisture.

Labelling. Label it to indicate nominal K-Value.