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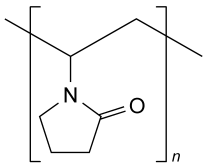
CROSPOVIDONE

Crospovidonum



$(C_6H_9NO)_n$ M_r $(111.1)_n$

[9003-39-8]

DEFINITION

Cross-linked homopolymer of 1-ethenylpyrrolidin-2-one.

Content: 11.0 per cent to 12.8 per cent of N (A_r 14.01) (dried substance).

CHARACTERS

Appearance: hygroscopic, white or yellowish-white powder or flakes.

2 types of crospovidone are available, depending on the particle size: type A and type B.

Solubility: practically insoluble in water, in ethanol 96 per cent and in methylene chloride.

IDENTIFICATION

A. Infrared absorption spectrophotometry (*2.2.24*).

Comparison: *crospovidone CRS*.

B. Suspend 1 g in 10 ml of *water R*, add 0.1 ml of *0.05 M iodine* and shake for 30 s. Add 1 ml of *starch solution R* and shake. No blue colour develops within 30 s.

C. To 10 ml of *water R*, add 0.1 g and shake. A suspension is formed and no clear solution is obtained within 15 min.

D. *The analytical screens must be clean and dry. For this purpose the screens are washed in hot water and allowed to dry overnight in a drying cabinet at 105 °C.*

Place 20 g in a 1000 ml conical flask, add 500 ml of *water R* and shake the suspension for 30 min. Pour the suspension through a 63 µm analytical screen, previously tared, and rinse the screen with *water R* until the filtrate is clear. Dry the screen and sample residue at 105 °C for 5 h in a drying cabinet without circulating air. Cool in a desiccator for 30 min and weigh.

Calculate the percentage screening residue (fraction of sample particles having a diameter of more than 63 µm), using the following expression:

$$\frac{m_1 - m_3}{m_2} \times 100$$

m_1 = mass of the screen and sample residue, after drying for 5 h, in grams;

m_2 = mass of the sample, in grams;

m_3 = mass of the screen, in grams.

If the screening residue fraction is more than 15 per cent, the substance is classified as type A; if the screening residue fraction is less than or equal to 15 per cent, the substance is classified as type B.

TESTS

Peroxides. Type A: maximum 400 ppm expressed as H_2O_2; type B: maximum 1000 ppm expressed as H_2O_2.

Suspend 2.0 g in 50 ml of *water R*. To 25 ml of this suspension add 2 ml of *titanium trichloride-sulphuric acid reagent R*. Allow to stand for 30 min and filter. The absorbance (*2.2.25*) of the filtrate, measured at 405 nm using a mixture of 25 ml of a filtered 40 g/l suspension of the substance to be examined and 2 ml of a 13 per cent *V/V* solution of *sulphuric acid R* as the compensation liquid, has a maximum of 0.35.

For type B use 10 ml of the suspension and dilute to 25 ml with *water R* for the test.

Water-soluble substances: maximum 1.0 per cent.

Place 25.0 g in a 400 ml beaker, add 200 ml of *water R* and stir for 1 h using a magnetic stirrer. Transfer the suspension to a 250.0 ml volumetric flask, rinsing with *water R*, and dilute to volume with the same solvent. Allow the bulk of the solids to settle. Filter about 100 ml of the almost clear supernatant liquid through a membrane filter (nominal pore size 0.45 µm), protected by superimposing a membrane filter (nominal pore size 3 µm). While filtering, stir the liquid above the membrane filter manually or by means of a mechanical stirrer, taking care not to damage the membrane filter. Transfer 50.0 ml of the clear filtrate to a tared 100 ml beaker, evaporate to dryness and dry at 105-110 °C for 3 h. The residue weighs a maximum of 50 mg.

Impurity A. Liquid chromatography (*2.2.29*).

Test solution. Suspend 1.250 g in 50.0 ml of *methanol R* and shake for 60 min. Leave the bulk to settle and filter through a filter membrane (nominal pore size 0.2 µm).

Reference solution (a). Dissolve 50 mg of *1-vinylpyrrolidin-2-one R* (impurity A) in *methanol R* and dilute to 100.0 ml with the same solvent. Dilute 1.0 ml of this solution to 100.0 ml with *methanol R*. Dilute 5.0 ml of this solution to 100.0 ml with the mobile phase.

Reference solution (b). Dissolve 10 mg of *1-vinylpyrrolidin-2-one R* (impurity A) and 0.50 g of *vinyl acetate R* in *methanol R* and dilute to 100 ml with the same solvent. Dilute 1.0 ml of this solution to 100.0 ml with the mobile phase.

Precolumn:

– *size*: *l* = 0.025 m, Ø = 4 mm;
– *stationary phase*: *octadecylsilyl silica gel for chromatography R* (5 µm).

Column:

– *size*: *l* = 0.25 m, Ø = 4 mm;
– *stationary phase*: *octadecylsilyl silica gel for chromatography R* (5 µm);
– *temperature*: 40 °C.

Mobile phase: *acetonitrile R, water R* (10:90 *V/V*).

Flow rate: adjusted so that the retention time of the peak due to impurity A is about 10 min.

Detection: spectrophotometer at 235 nm.

Injection: 50 µl. After each injection of the test solution, wash the precolumn by passing the mobile phase backwards, at the same flow rate as applied in the test, for 30 min.

System suitability:

– *resolution*: minimum 2.0 between the peaks due to impurity A and vinyl acetate in the chromatogram obtained with reference solution (b);
– *repeatability*: maximum relative standard deviation of 2.0 per cent after 5 injections of reference solution (a).

Limits:

– *impurity A*: not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (10 ppm).

Heavy metals (*2.4.8*): maximum 10 ppm.

2.0 g complies with test D. Prepare the reference solution using 2 ml of *lead standard solution (10 ppm Pb) R*.

Loss on drying (*2.2.32*): maximum 5.0 per cent, determined on 0.500 g by drying in an oven at 105 °C.

Sulphated ash (*2.4.14*): maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Place 100.0 mg of the substance to be examined (*m* mg) in a combustion flask and add 5 g of a mixture of 1 g of *copper sulphate R*, 1 g of *titanium dioxide R* and 33 g of *dipotassium sulphate R*, and 3 glass beads. Wash any adhering particles from the neck into the flask with a small quantity of *water R*. Add 7 ml of *sulphuric acid R*, allowing it to run down the insides of the flask, and mix the contents by rotation. Close the mouth of the flask loosely, for example by means of a glass bulb with a short stem, to avoid excessive loss of sulphuric acid. Heat gradually at first, then increase the temperature until there is vigorous boiling with condensation of sulphuric acid in the neck of the flask; precautions are to be taken to prevent the upper part of the flask from becoming overheated. Continue the heating for 45 min. Cool, dissolve the solid material by cautiously adding 20 ml of *water R* to the mixture, cool again and place in a steam-distillation apparatus. Add 30 ml of *strong sodium hydroxide solution R* through the funnel, rinse the funnel cautiously with 10 ml of *water R* and distil immediately by passing steam through the mixture. Collect 80-100 ml of distillate in a mixture of 30 ml of a 40 g/l solution of *boric acid R* and 0.05 ml of *bromocresol green-methyl red solution R* and enough *water R* to cover the tip of the condenser. 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 R*. Titrate the distillate with *0.025 M sulphuric acid* until the colour of the solution changes from green through pale greyish-blue to pale greyish-red-purple (n_1 ml of *0.025 M sulphuric acid*).

Repeat the test using about 100 mg of *glucose R* in place of the substance to be examined (n_2 ml of *0.025 M sulphuric acid*).

Percentage content of nitrogen:

$$\frac{0.7004\,(n_1 - n_2)}{m} \times 100$$

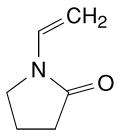
STORAGE

In an airtight container.

LABELLING

The label states the type (type A or type B).

IMPURITIES



A. 1-ethenylpyrrolidin-2-one (1-vinylpyrrolidin-2-one).

FUNCTIONALITY-RELATED CHARACTERISTICS

This section provides information on characteristics that are recognised as being relevant control parameters for one or more functions of the substance when used as an excipient (see chapter 5.15). This section is a non-mandatory part of the monograph and it is not necessary to verify the characteristics to demonstrate compliance. Control of these characteristics can however contribute to the quality of a medicinal product by improving the consistency of the manufacturing process and the performance of the medicinal product during use. Where control methods are cited, they are recognised as being suitable for the purpose, but other methods can also be used. Wherever results for a particular characteristic are reported, the control method must be indicated.

The following characteristics may be relevant for crospovidone used as disintegrant.

Hydration capacity. Introduce 2.0 g into a 100 ml centrifuge tube and add 40 ml of *water R*. Shake vigorously until a suspension is obtained. Shake again 5 min and 10 min later, then centrifuge for 15 min at 750 *g*. Decant the supernatant liquid and weigh the residue. The hydration capacity is the ratio of the mass of the residue to the initial mass of the sample. It is typically 3 to 9.

Particle-size distribution (*2.9.31*).

Powder flow (*2.9.36*).

The following characteristic may be relevant for crospovidone used as suspension stabiliser.

Settling volume. Introduce 10 g into a 100 ml graduated cylinder and add 90 ml of *water R*. Shake vigorously. Dilute to 100 ml with *water R*, washing the powder residues from the walls of the cylinder. Allow to stand for 24 h, then read the volume of the sediment. It is typically greater than 60 ml.