BRIEFING NOTE

CROSPOVIDONE

(Stage 4 Revision 2 – CP: EP)

IDENTIFICATION D

Identifying the type of crospovidone is necessary for selecting the limit of the test for peroxides. The method proposed here is not a tool to determine the particle size distribution; in the latter case, the laser diffraction method would be more appropriate. The wet sieving method allows the distinction between crospovidone type A and type B.

The microscopic method proved to be highly subjective since it is very dependent on sampling, sample preparation and the area under the microscope selected for examination.

Comparative testing has been carried out using the dry sieving method and the air-jet sieving method; the following results were obtained:

	Crospovidone type A	Crospovidone type B
Air-jet sieving	35 % passed through a 63 µm sieve	84 % passed through a 63 µm sieve
Dry sieving	36 % passed through a 63 µm sieve	77 % passed through a 63 µm sieve

In both cases the behaviour of crospovidone type A was satisfactory and the results were as expected. Due to electrostatic charges, the results obtained with crospovidone type B are much lower than expected (77 to 84%) whereas a result close to 100% would be normal for a micronised powder (particle size mainly lower than 50 µm).

These results show that the dry-sieving and the jet-sieving methods are not appropriate for the determination of the type of crospovidone. On the contrary, the wet sieving method removes these subjective variables from the classification of crospovidone and the results obtained for crospovidone type B are closed to 100% (see letters from BASF and ISP previously supplied to PDG).

IPEC provided EP with the wet sieving method in June 2006 and informed that a consensus existed about it between the two manufacturers BASF and ISP. BASF is the originator of this method; IPEC added that the latter was regarded as industry compliant.

The following limits were proposed by BASF, ISP and IPEC:

- if the screen residue fraction is more than 15 per cent the substance is classified as type A;
- if the screen residue fraction is less of equal to 15 per cent, the substance is classified as type B.

It is proposed to retain these method and limits for the international harmonisation text (see also method and validation data, results from BASF and from ISP provided to PDG in previous letters since September 2008).

During the PDG-TriPEC meeting held in Brussels last November, TriPEC re-emphasised their acceptance of the method.

In answer to JP concerns, the definition of m_2 has been modified.

TESTS

Rationale for not including tests for aldehydes, hydrazine, formic acid and 2-pyrrolidone: during the manufacturing process, crospovidone, which is insoluble in water, is washed with water after polymerisation in such a way that these impurities are no longer found in the product or they are found at a very low level.

Therefore their control is not deemed necessary. Neither BASF or ISP control these impurities in crospovidone.

CROSPOVIDONE

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

DEFINITION

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

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

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

IDENTIFICATION

A. 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.

B. 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.

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

Place 20 g (m_2) calculated on the dried substance 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 sieve, previously tared, and rinse the sieve with *water R* until the filtrate is clear. Dry the sieve 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 sieving residue fraction of sample particles having a diameter of more than 63 µm, in percentage, using the following expression:

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

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

m_2 = initial mass of the sample, calculated on a dried basis, in grams;

m_3 = mass of the sieve, in grams.

If the sieving residue fraction is more than 15 per cent, the substance is classified as type A; if the sieving 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 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 diluted to 25 ml with *water R* for the test.

Water-soluble substances: maximum 1.5 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 0.45 µm membrane filter, protected by superimposing a 3 µm membrane filter. While filtering, stir the liquid above the filter manually or by means of a mechanical stirrer, taking care not to damage the 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 75 mg.

Impurity A. Liquid chromatography.

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 0.2 µm filter.

Reference solution (a). Dissolve 50 mg of *1-vinylpyrrolidin-2-one R* in *methanol R* and dilute to 100.0 ml with the same solvent. Dilute 1.0 ml of the 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* 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) [1].

Column:

- *size*: *l* = 0.25 m, Ø = 4 mm;

- *stationary phase*: *octadecylsilyl silica gel for chromatography R* (5 µm)[2];

- *temperature*: 40 °C.

[1] Nucleosil 120-5 C18 from Macherey & Nagel
[2] Aquasil C18 from ThermoHypersil.

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

Flow rate: 1.0 ml/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 6 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).

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

Sulphated ash: maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Place 0.100 g 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 inside wall of the flask.

Gradually heat the flask until the solution has a clear, yellowish-green colour, and the inside wall of the flask is free from carbonised material, and then heat for a further 45 min. After cooling, cautiously add 20 ml of *water R*, and connect the flask to the distillation apparatus previously washed by passing steam through it. To the absorption flask add 30 ml of a 40 g/l solution of *boric acid R*, 3 drops of *bromocresol green-methyl red solution R* and sufficient *water R* to immerse the lower end of the condenser tube. Add 30 ml of a solution of *strong sodium hydroxide solution R* through a funnel, cautiously rinse the funnel with 10 ml of *water R*, immediately close the clamp attached to the rubber tube, then start the distillation with steam to obtain 80-100 ml of distillate. Remove the absorption flask from the lower end of the condenser tube, rinsing the end part with a small quantity of *water R*, and titrate the distillate with *0.025 M sulphuric acid* until the color of the solution changes from green through pale greyish-blue to pale greyish red-purple. Carry out a blank determination and make any necessary correction.

1 ml of *0.025 M sulphuric acid* is equivalent to 0.700 mg of N.

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).

REAGENTS

1-Vinylpyrrolidin-2-one. C_6H_9NO. (M_r 111.1). [88-12-0]. 1-Ethenylpyrrolidin-2-one.

Content: minimum 99.0 per cent of C_6H_9NO.

A clear colourless liquid.

Water (Karl Fisher): maximum 0.1 per cent, determined on 2.5 g. Use as the solvent, a mixture of 50 ml of anhydrous methanol R and 10 ml of butyrolactone R.

Assay. Examine by gas chromatography.

The chromatography may be carried out using

— a fused-silica column 30 m long and 0.5 mm in internal diameter the inner wall of which is coated with a 1.0 µm layer of macrogol 20 000 R,

— helium for chromatography R as the carrier gas,

— a flame-ionisation detector,

maintaining the temperature of the injection port at 190 °C and programming the temperature of the column as follows: maintain the temperature at 80 °C for 1 min and then increase it to 190 °C at a rate of 10 °C per minute. Maintain at 190 °C for 15 min. Inject 0.3 µl of the substance to be examined and adjust the flow rate of the carrier gas so that the retention time of the peak corresponding to 1-vinylpyrrolidin-2-one is about 17 min. Determine the content of C_6H_9NO by internal normalisation.