BRIEFING

Microcrystalline Cellulose, *NF 22* page 2845 and page 1305 of *PF* 29(4) [July–Aug. 2003]. The United States Pharmacopeia is the coordinating pharmacopeia for the international harmonization of the compendial standards for the *Microcrystalline Cellulose* monograph, as part of the process of international harmonization of monographs and general analytical methods of the European, Japanese, and United States pharmacopeias. The following monograph, which represents the **ADOPTION STAGE 6** document, is based on corresponding monograph for *Microcrystalline Cellulose* that was prepared by the U.S. Pharmacopeia. This draft was based in part on comments from the European and Japanese Pharmacopoeias in response to the Provisional Harmonized Text Stage 5A and 5B drafts.

Pharmacopeial Discussion Group Sign-Off Document

Attributes	EP	JP	USP
Definition	+	+	+
Labeling	–	+	+
Identification A	+	+	+
Identification B	+	+	+
Conductivity	+	+	+
pH	+	+	+
Loss on drying[1]	+	+	+
Residue on ignition	+	+	+
Bulk density[2]	–	+	+
Water-soluble substances	+	+	+
Ether-soluble substances	+	+	+

1 USP will retain, as a specific local attribute, that the value can be within a percentage range, as specified within the labeling.

2 USP will retain, as a specific local attribute, that the bulk density value is wthin the labeled specification.

Legend: + will adopt and implement; – will not stipulate.

Nonharmonized attributes: Characters, Heavy metals, Microbial limits, Labeling, Packaging and storage.

Specific local attributes: JP: Identification C—Dispersion test; USP: Organic volatile impurities, Particle size distribution estimation by analytical sieving.

Reagents and reference materials: Each pharmacopeia will adapt the text to take account of local reference materials and reagent specifications.

Differences between the Adoption Stage 6 document and the current *NF* monograph include the following:

1. Definition—No change.
2. *Packaging and storage*— No change.
3. *Labeling*— Additional information is presented to clarify particle size testing.
4. *Identification* test *B*— The requirements to be within the labeled specification are deleted.
5. *Microbial limits*— No change.
6. *Conductivity*— No change.
7. *pH*— The upper limit is increased to 7.5 from 7.0 to conform to EP and JP standards and to be consistent with the monograph for *Powdered Cellulose*.
8. *Loss on drying*— No change.
9. *Residue on ignition*— The standard for this test was increased to not more than 0.1%, which conforms to EP standards.
10. *Bulk density*— No change.
11. *Water-soluble substances*— The standard for this test was changed from 0.24% to 0.25%.
12. *Ether-soluble substances*— No change.
13. *Heavy metals*— No change.
14. *Organic volatile impurities*— No change.
15. *Particle size distribution estimation by analytical sieving*— To further strengthen the monograph, a test for the determination of particle size distribution is added. Because the determination of particle size distribution is not a compendial requirement for this article, the test does not contain limit values. The test provides a means for ensuring that suppliers and users of Microcrystalline Cellulose who have an interest in this property may obtain this value by the same method. Users who do not require any definite particle size range material obviously would have no concern about this material property or monograph test.

(EMC: J. Lane) RTS—41235-8

Change to read:

~~**Microcrystalline Cellulose**~~

~~Cellulose.~~
~~Cellulose [*9004-34-6*].~~

» Microcrystalline Cellulose is purified, partially depolymerized cellulose prepared by treating alpha cellulose, obtained as a pulp from fibrous plant material, with mineral acids.

Packaging and storage— Preserve in tight containers.

Labeling— The labeling indicates the nominal loss on drying, bulk density, and degree of polymerization values. Degree of polymerization compliance is determined using *Identification* test *B.* Where the particle size distribution is stated in the labeling, the labeling indicates the d_{10}, d_{50}, and d_{90} values and the range for each.

Identification—

A: Prepare iodinated zinc chloride solution by dissolving 20 g of zinc chloride and 6.5 g of potassium iodide in 10.5 mL of water. Add 0.5 g of iodine, and shake for 15 minutes. Place about 10 mg of Microcrystalline Cellulose on a watch glass, and disperse in 2 mL of iodinated zinc chloride solution: the substance takes on a violet-blue color.

B: Transfer 1.3 g of Microcrystalline Cellulose, accurately weighed to 0.1 mg, to a 125-mL conical flask. Add 25.0 mL of water and 25.0 mL of 1.0 M cupriethylenediamine hydroxide solution. Immediately purge the solution with nitrogen, insert the stopper, and shake on a wrist action shaker or other suitable mechanical shaker until completely dissolved. Transfer 7.0 mL of the solution to a calibrated number 150 Cannon-Fenske or equivalent [1] viscosimeter. Allow the solution to equilibrate at 25 ± 0.1° for not less than 5 minutes. Time the flow between the 2 marks on the viscosimeter, and record the flow time, t_1, in seconds. Calculate the kinematic viscosity, $(KV)_1$, of the Microcrystalline Cellulose taken by the formula:

$$t_1(k_1),$$

in which k_1 is the viscosimeter constant (see *Viscosity* ⟨911⟩). Obtain the flow time, t_2, for a 0.5 *M* cupriethylenediamine hydroxide solution using a number 100 Cannon-Fenske or equivalent [1] viscosimeter. Calculate the kinematic viscosity, $(KV)_2$, of the solvent by the formula:

$$t_2(k_2),$$

in which k_2 is the viscosimeter constant. Determine the relative viscosity, η_{rel}, of the Microcrystalline Cellulose specimen taken by the formula:

$$(KV)_1/(KV)_2.$$

Determine the intrinsic viscosity, $[\eta]$ *c,* by interpolation, using the *Intrinsic Viscosity Table* in the *Reference Tables* section. Calculate the degree of polymerization, *P,* by the formula:

$$((95)[\eta]c)/(W_S[(100 - \%LOD)/100]),$$

in which W_S is the weight, in g, of the Microcrystalline Cellulose taken, and % *LOD* is the value obtained from the test for *Loss on drying.* The degree of polymerization is not greater than 350, and is within the labeled specification.

Microbial limits ⟨61⟩ — The total aerobic microbial count does not exceed 1000 cfu per g, the total combined molds and yeasts count does not exceed 100 cfu per g, and it meets the requirements of the tests for absence of *Staphylococcus aureus* and *Pseudomonas aeruginosa* and for absence of *Escherichia coli* and *Salmonella* species.

Conductivity— Shake about 5 g with 40 mL of water for 20 minutes, and centrifuge. Retain the supernatant liquid for use in the *pH* test. Using an appropriate conductivity meter that has been standardized with a potassium chloride conductivity calibration standard [2] having a conductivity of 100 µS per cm, measure the conductivity of the supernatant solution after a stable reading is obtained, and measure the conductivity of the water used to prepare the test specimen. The conductivity of the supernatant solution does not exceed the conductivity of the water by more than 75 µS per cm.

pH ⟨791⟩ **:** between 5.0 and 7.0 in the supernatant solution obtained in the *Conductivity* test.

Loss on drying ⟨731⟩ — Dry it at 105° for 3 hours: it loses not more than 7.0% of its weight, or some other lower percentage, or is within a percentage range, as specified in the labeling.

Residue on ignition ⟨281⟩ **:** not more than 0.05%.

Bulk density— Use a volume meter [3] that has been fitted with a 10-mesh screen. The volume meter is freestanding of the brass or stainless steel cup, which is calibrated to a capacity of 25.0 ± 0.05 mL and has an inside diameter of 30.0 ± 2.0 mm. Weigh the empty cup, position it under the chute, and slowly pour the powder from a height of 5.1 cm (2 inches) above the funnel through the volume meter, at a rate suitable to prevent clogging, until the cup overflows. [NOTE— If excessive clogging of the screen occurs, remove the screen.] Level the excess powder, and weigh the filled cup. Calculate the bulk density by dividing the weight of the powder in the cup by the volume of the cup: the bulk density is within the labeled specification.

Water-soluble substances— Shake 5.0 g with about 80 mL of water for 10 minutes, filter with the aid of vacuum through filter paper (Whatman No. 42 or equivalent) into a vacuum flask. Transfer the filtrate to a tared beaker, evaporate to dryness without charring, dry at 105° for 1 hour, cool in a desiccator, and weigh: the difference between the weight of the residue and the weight obtained from a blank determination does not exceed 12.0 mg (0.24%).

Ether-soluble substances— Place 10.0 g in a chromatography column having an internal diameter of about 20 mm, and pass 50 mL of peroxide-free ether through the column. Evaporate the eluate to dryness in a previously dried and tared evaporating dish with the aid of a current of air in a fume hood. After all the ether has evaporated, dry the residue at 105° for 30 minutes, cool in a desiccator, and weigh: the difference between the weight of the residue and the weight obtained from a blank determination does not exceed 5.0 mg (0.05%).

Heavy metals, *Method II* ⟨231⟩ **:** 0.001%.

Organic volatile impurities, *Method IV* ⟨467⟩ **:** meets the requirements.

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[1] A Ubbelohde 1C viscosimeter is equivalent to a Cannon-Fenske 150 viscosimeter. A Ubbelohde 1 viscosimeter is equivalent to a Cannon-Fenske 100 viscosimeter.

[2] Commercially available conductivity calibration solutions for conductivity meter standardization, standardized by methods traceable to the National Institute of Science and Technology (NIST), may be used. Solutions prepared according to instructions given in ASTM Standard D1125 may be used provided the conductivity of the resultant solution is the same as that of the solution prepared from the NIST certified material.

[3] A suitable apparatus is described as the Scott Volumeter in ASTM B 329, available from the American Society for Testing and Materials, 100 Barr Harbor Drive, West Conshohocken, PA 19429-2959.

Auxiliary Information—*Staff Liaison* : Justin Lane, B.S., Scientific Associate
Expert Committee : (EMC) Excipients: Monograph Content
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Phone Number : 1-301-816-8323

Add the following:

■ **Microcrystalline Cellulose**

Cellulose.
Cellulose [*9004-34-6*].

» Microcrystalline Cellulose is purified, partially depolymerized cellulose prepared by treating alpha cellulose, obtained as a pulp from fibrous plant material, with mineral acids.

Packaging and storage— Preserve in tight containers.

Labeling— The labeling indicates the nominal loss on drying, bulk density, and degree of polymerization values. Degree of polymerization compliance is determined using *Identification* test *B*. Where the particle size distribution is stated in the labeling, proceed as directed under *Particle Size Distribution Estimation by Analytical Sieving* ⟨786⟩ ; the labeling indicates the d_{10} , d_{50} , and d_{90} values (see *Powder Fineness* ⟨811⟩) and the range for each.

Identification—

A: Prepare iodinated zinc chloride solution by dissolving 20 g of zinc chloride and 6.5 g of potassium iodide in 10.5 mL of water. Add 0.5 g of iodine, and shake for 15 minutes. Place about 10 mg of Microcrystalline Cellulose on a watch glass, and disperse in 2 mL of iodinated zinc chloride solution: the substance takes on a violet-blue color.

B: Transfer 1.3 g of Microcrystalline Cellulose, accurately weighed to 0.1 mg, to a 125-mL conical flask. Add 25.0 mL of water and 25.0 mL of 1.0 M cupriethylenediamine hydroxide solution. Immediately purge the solution with nitrogen, insert the stopper, and shake on a wrist action shaker or other suitable mechanical shaker until completely dissolved. Transfer 7.0 mL of the solution to a calibrated number 150 Cannon-Fenske, or equivalent, viscosimeter. Allow the solution to equilibrate at 25 ± 0.1° for not less than 5 minutes. Time the flow between the two marks on the viscosimeter, and record the flow time, t_1 , in seconds. Calculate the kinematic viscosity, $(KV)_1$, of the Microcrystalline Cellulose taken by the formula:

$$t_1 (k_1),$$

in which k_1 is the viscosimeter constant (see *Viscosity* ⟨911⟩). Obtain the flow time, t_2 , for a 0.5 M cupriethylenediamine hydroxide solution using a number 100 Cannon-Fenske, or equivalent, viscosimeter. Calculate the kinematic viscosity, $(KV)_2$, of the solvent by the formula:

$$t_2 (k_2),$$

in which k_2 is the viscosimeter constant. Determine the relative viscosity, η_{rel}, of the Microcrystalline Cellulose specimen taken by the formula:

$$(KV)_1 / (KV)_2.$$

Determine the intrinsic viscosity, $[\eta]c$, by interpolation, using the *Intrinsic Viscosity Table* in the *Reference Tables* section. Calculate the degree of polymerization, *P,* by the formula:

$$(95)[\eta]c / W_S [(100 - \%LOD)/100],$$

in which W_S is the weight, in g, of the Microcrystalline Cellulose taken; and % *LOD* is the value obtained from the test for *Loss on drying.* The degree of polymerization is not greater than 350.

Microbial limits ⟨61⟩ **—** The total aerobic microbial count does not exceed 1000 cfu per g, the total combined molds and yeasts count does not exceed 100 cfu per g, and it meets the requirements of the tests for absence of *Staphylococcus aureus* and *Pseudomonas aeruginosa* and for absence of *Escherichia coli* and *Salmonella* species.

Conductivity— Shake about 5 g with 40 mL of water for 20 minutes, and centrifuge. Retain the supernatant for use in the *pH* test. Using an appropriate conductivity meter that has been standardized with a potassium chloride conductivity calibration standard having a conductivity of 100 µS per cm, measure the conductivity of the supernatant after a stable reading is obtained, and measure the conductivity of the water used to prepare the test specimen. The conductivity of the supernatant does not exceed the conductivity of the water by more than 75 µS per cm.

pH ⟨791⟩ **:** between 5.0 and 7.5 in the supernatant obtained in the *Conductivity* test.

Loss on drying ⟨731⟩ **—** Dry it at 105° for 3 hours: it loses not more than 7.0% of its weight, or some other lower percentage, or is within a percentage range, as specified in the labeling.

Residue on ignition ⟨281⟩ **:** not more than 0.1%.

Bulk density— Use a volumeter that has been fitted with a 10-mesh screen. The volumeter is freestanding of the brass or stainless steel cup, which is calibrated to a capacity of 25.0 ± 0.05 mL and has an inside diameter of 30.0 ± 2.0 mm. Weigh the empty cup, position it under the chute, and slowly pour the powder from a height of 5.1 cm (2 inches) above the funnel through the volumeter, at a rate suitable to prevent clogging, until the cup overflows. [NOTE— If excessive clogging of the screen occurs, remove the screen.] Level the excess powder, and weigh the filled cup. Calculate the bulk density by dividing the weight of the powder in the cup by the volume of the cup: the bulk density is within the labeled specification.

Particle size distribution estimation by analytical sieving ⟨786⟩ **—** [NOTE— In cases where there are no functionality-related concerns regarding the particle size distribution of the article, this test may be omitted.] Where the labeling states the particle size distribution, determine the particle size distribution as directed in the chapter.

Water-soluble substances— Shake 5.0 g with about 80 mL of water for 10 minutes, filter with the aid of vacuum through filter paper (Whatman No. 42 or equivalent) into a vacuum flask. Transfer the filtrate to a tared beaker, evaporate to dryness without charring, dry at 105° for 1 hour, cool in a desiccator, and weigh: the difference between the weight of the residue and the weight obtained from a blank determination does not exceed 12.5 mg (0.25%).

Ether-soluble substances— Place 10.0 g in a chromatographic column having an internal diameter of about 20 mm, and pass 50 mL of peroxide-free ether through the column. Evaporate the eluate to dryness in a previously dried and tared evaporating dish with the aid of a current of air in a fume hood. After all the ether has evaporated, dry the residue at 105° for 30 minutes, cool in a desiccator, and weigh: the difference between the weight of the residue and the weight obtained from a blank determination does not exceed 5.0 mg (0.05%).

Heavy metals, *Method II* ⟨231⟩ **:** 0.001%.

Organic volatile impurities, *Method IV* ⟨467⟩ **:** meets the requirements. ■1S (*NF23*)

Auxiliary Information—*Staff Liaison* : Justin Lane, B.S., Scientific Associate

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