PHARMACOPEIAL DISCUSSION GROUP
CORRECTION
CODE: E-20

NAME: HYDROXYPROPYLCELLULOSE, LOW SUBSTITUTED

Correction 3 (previous sign-off on 15 November 2021)

Items to be corrected:
- CAS number.
- Assay: detailed vial and heater block dimensions removed.
- Heavy metals: JP local requirement test deleted.

Harmonised attributes:

Attribute	EP	JP	USP
Definition	+	+	+
Identification A	+	+	+
Identification B	+	+	+
Identification C	+	+	+
pH	+	+	+
Loss on drying	+	+	+
Residue on ignition	+	+	+
Assay for hydroxypropoxy groups	+	+	+
Packaging and Storage	+	+	+

Legend
+ will adopt and implement; – will not stipulate

Non-harmonised attributes:
Characters/Description

Local requirements

EP	JP	USP
Functionality-Related Characteristics (Settling volume, Degree of substitution (Assay for hydroxypropoxy groups)*, Particle-size distribution)	None	Chloride

* Degree of substitution (Assay for hydroxypropoxy groups) is a harmonised attribute. It is also included in the Functionality-Related Characteristics section of the EP monograph.

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

European Pharmacopoeia

Signature	Name	Date
DocuSigned by: Petra Doerr 82DD39EBFD74446...	Petra Doerr	20.12.2022

Japanese Pharmacopoeia

Signature	Name	Date
Y. Goda for Y. Yoshida	Yukihiro Goda	20 Jan, 2023

United States Pharmacopeia

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CP: EP
December 2022

E20 - Hydroxypropyl Cellulose, Low Substituted

Stage 3B

DEFINITION

Cellulose, 2-hydroxypropyl ether *[9004-64-2].*

Hydroxypropyl Cellulose, Low substituted, is a low- substituted *O*-(2-hydroxypropylated) cellulose. It contains not less than 5.0 percent and not more than 16.0 percent of hydroxypropoxy groups, calculated on the dried basis.

Packaging and storage—Preserve in tight containers.

Identification—

A: Infrared absorption spectrophotometry.
Record the infrared absorption spectrum of *Hydroxypropylcellulose, Low-substituted* and compare with the Reference Spectrum or the spectrum obtained with the Reference Standard: the transmission minima correspond in position and relative size.

B: Shake thoroughly 0.1 g with 10 mL of water. It does not dissolve.

C: To the suspension obtained in Identification B, add 1 g of sodium hydroxide, and shake until it becomes homogeneous. Transfer 5 mL to a suitable container, add 10 mL of a mixture of acetone and methanol (4:1), and shake: a white, flocculent precipitate is formed.

pH between 5.0 and 7.5, in a suspension of 1.0 g prepared by evenly distributing the powder with 100 mL of carbon dioxide free water stirring the mixture with a magnetic stirrer.

Loss on drying : Dry 1 g at 105° for 1 hour: it loses not more than 5.0% of its weight.

Residue on ignition : not more than 0.8% on 1.0 g.

Assay for hydroxypropoxy groups—Gas Chromatography

(i) Apparatus – Reaction vial: A 5 mL pressure-tight serum vial, equipped with a pressure-tight septum having a polytetrafluoroethylene-faced butyl rubber, and air-tight sealing by an aluminum crimp or another sealing system providing a sufficient air-tightness.
Heater: A heating module with a square-shape aluminum block having holes so that the reaction vials fits, capable of mixing the contents of the vial using a magnetic stirrer equipped in the heating module or using a reciprocal shaker which performs reciprocating motion of approximately 100 times per minute.

(ii) Procedure – Weigh accurately about 0.065 g of Hydroxypropyl Cellulose, Low Substituted, place in a reaction vial, add 0.06 to 0.10 g of adipic acid, 2.0 mL of the internal standard solution and 2.0 mL of hydroiodic acid (typically the concentration is 57 %), immediately cap and seal the vial, and weigh accurately. Using a magnetic stirrer equipped in the heating module, or using a reciprocal shaker, mix the contents of the vial continuously for 60 minutes while heating the block so that the temperature of the contents is maintained at 130±2℃. If a reciprocal shaker or magnetic stirrer cannot be used, shake the vial well by hand at 5-minute intervals during the initial 30 minutes of the heating time. Allow the vial to cool, and again weigh accurately. If the weight loss is less than 26 mg and there is no evidence of a leak, use the upper layer of the mixture as the sample solution. Separately, take 0.06 to 0.10 g of adipic acid, 2.0 mL of the internal standard solution and 2.0 mL of hydroiodic acid in another reaction vial, cap and seal the vial, and weigh accurately. Add 15 to 22 µL of isopropyl iodide for assay through the septum with a syringe, weigh accurately. Shake the reaction vial well, and use the upper layer of the contents as the standard solution.

Internal standard solution – A solution of *n*-octane in *o*-xylene (3 in 100).

Operating conditions -

Detector: A thermal conductivity detector or hydrogen flame- ionization detector.

Column: Fused silica, 0.53 mm inside diameter and 30 m in length, coated with 3 µm 100% dimethyl polysiloxane for gas chromatography. Use a guard column if necessary.

Carrier gas: Helium

Flow Rate: Adjust the flow rate so the retention time of the internal standard is about–10 minutes (4.3 mL/min).

Split ratio: 1:40

Injection Volume: 1-2 µL

Temperature:

— *temperature program a*s follows:

	Time (min)	**Temperature (C)**
Column	0-3	50
	3-8	50 → 100
	8-12.3	100 → 250
	12.3-20.3	250
Injection port		250
Detector		280

Relative retention (with reference to *n*-octane retention time = about 8 min): isopropyl iodide = about 0.8

System Suitability:

System performance:

Resolution: Not less than 5 between isopropyl iodide and *n*-octane.

System repeatability:

Relative standard deviation: NMT 2.0%, using the peak area ratio between isopropyl iodide and the internal standard for six injections.

Calculate the ratios, Q_T of the peak area of isopropyl iodide from the sample solution to that of the internal standard, and Q_S of the peak area of isopropyl iodide from the standard solution to that of the internal standard.

Content (%) of hydroxypropoxyl group = $Q_T/Q_S \times W_S/W \times 44.17$

W_S: Amount (mg) of isopropyl iodide in the standard solution.

W: Amount (mg) of the sample, calculated on the dried basis.

44.17 = Molar mass of hydroxypropoxy group / Molar mass of isopropyl iodide group x100

Reagents:

Isopropyl iodide, $(CH_3)_2CHI$, *MW* 169.99, *[75-30-9]*--- Use a suitable grade, assay ≥ 99%

n-octane, $CH_3(CH_2)_6CH_3$, *MW* 114.23, *[111-65-9]*--- Use a suitable grade, assay ≥ 99.0%