PHARMCOPEIAL DISCUSSION GROUP

CODE: E-22

NAME: HYPROMELLOSE PHTHALATE

Correction 1 (previous sign-off on 2006-06-06)

Item to be corrected:

- Chloride: Add a requirement to allow each solution to stand for 5 min, protected from direct sunlight after mixing with 1 mL of silver nitrate TS (0.07%).
- Limit of free phthalic acid: Specify five (5) replicate injections for system suitability - relative standard deviation (RSD) determination.

	Harmonized attributes		
	EP	JP	USP
Definition	+	+	+
Packaging and storage	+	+	+
Viscosity	+	+	+
Water	+	+	+
Residue on Ignition	+	+	+
Chloride	+	+	+
Limit of free phthalic acid	+	+	+
Phthalyl content	+	+	+

Legend
+ will adopt and implement; - will not stipulate

Non-harmonized attributes
Characters, Labeling, Identification (IR)

Local requirements

EP	JP	USP
Functionality-Related Characteristics (Viscosity*, Solubility, Phthalyl groups*)	Phthalic Acid, *System Suitability* – System performance, Heavy metals	None

* Viscosity and Phthalyl content/groups are harmonized attributes. They are also included in the Functionality-related Characteristics section of the EP monograph.

Reagents and reference materials
Each pharmacopeia will adopt the text to take account of local reference materials and reagent specifications.
Each pharmacopeia will consider actual titrant concentration in equations according to their local rules of calculation for titration.

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European Pharmacopoeia

Signature	Name	Date
P. Dörr	Petra Doerr	02/11/2021

Japanese Pharmacopoeia

Signature	Name	Date
Y. Goda for Y. Yoshida	Yakihiro Goda	15 Nov, 2021

United States Pharmacopoeia

Signature	Name	Date
T.	KEVIN MOORE	9-NOV. 2021

E22 Hypromellose Phthalate

Definition - Hypromellose Phthalate (Hydroxypropyl Methylcellulose Phthalate) is a monophthalic acid ester of hypromellose (hydroxypropyl methylcellulose). It contains methoxy ($-OCH_3$) and hydroxypropoxy ($-OCH_2CHOHCH_3$) groups and not less than 21.0 percent and not more than 35.0 percent of phthalyl (*o*-carboxybenzoyl, $C_8H_5O_3$) groups, calculated on the anhydrous basis.

Packaging and storage—Preserve in tight containers.

Viscosity —Dissolve 10 g, previously dried at 105° for 1 hour, in 90 g of a mixture of equal weights of methanol and methylene chloride by mixing and shaking: the viscosity, determined at 20 ± 0.1° (see *Procedure for Cellulose Derivatives* under *Viscosity general chapter in each pharmacopeia (e.g. USP* <911>), is not less than 80% and not more than 120% of that indicated by the label.

Water: not more than 5.0%.

Residue on ignition: not more than 0.20%. Ignition temperature 600 ± 50°

Chloride —Dissolve 1.0 g in 40 mL of 0.2 *N* sodium hydroxide, add 1 drop of phenolphthalein TS, and add 2 *N* nitric acid dropwise, with stirring, until the red color is discharged. Add an additional 20 mL of 2 *N* nitric acid with stirring. Heat on a water bath, with stirring, until the gel-like precipitate formed becomes granular. Cool the mixture, and centrifuge. Separate the liquid phase, and wash the residue with three successive 20-mL portions of water, separating the

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washings by centrifuging. Dilute the combined liquids with water to 200 mL, mix, and filter. A 50-ml, portion of the filtrate so obtained, after mixing with 1 mL of silver nitrate TS (0.07%) and allowing the solution to stand for 5 min, protected from direct sunlight, shows no more chloride than a control solution made by treating 0.50 ml of 0.01 *N* hydrochloric acid with 10 mL of 0.2 *N* sodium hydroxide, adding 7 mL of 2 *N* nitric acid, diluting with water to 50 mL, and adding 1 mL of silver nitrate TS (0.07%), which also allows the solution to stand for 5 min, protected from direct sunlight.

Limit of free phthalic acid—

Mobile phase—Prepare a filtered and degassed mixture of 0.1 % trifluoroacetic acid and acetonitrile (9:1). Make adjustments if necessary.

Standard solution—Transfer about 12.5 mg of phthalic acid, accurately weighed, to a 250-mL volumetric flask, add about 125 ml, of acetonitrile, and mix to dissolve. Add 25 mL of water, dilute with acetonitrile to volume, and mix.

Test solution—Transfer about 200 mg of Hypromellose Phthalate, accurately weighed, to a 100-mL volumetric flask, add about 50 mL of acetonitrile, and sonicate to dissolve partially. Add 10 mL of water, and sonicate to dissolve. Cool to room temperature, dilute with acetonitrile to volume, and mix.

Chromatographic system—The liquid chromatograph is equipped with a 235-nm detector and a 4.6-mm x 25-cm column that contains packing L1 with a high carbon load. The flow rate is about 2.0 mL per minute. Chromatograph the *Standard solution* and record the peak responses as directed under *Procedure*: the relative standard deviation for five (5) replicate injections is not more than 1.0%.

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Procedure—Separately inject equal volumes (about 10 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the peak responses. Calculate the percentage of phthalic acid in the portion of Hypromellose Phthalate taken by the formula:

$$10(C/W(r_U/r_S),$$

in which C is the concentration, in µg per mL, of phthalic acid in the *Standard solution*, W is the weight, in mg, on the anhydrous basis, of Hypromellose Phthalate taken to prepare the *Test solution*, and r_U and r_S are the phthalic acid peak responses obtained from the *Test solution* and the *Standard solution*, respectively: not more than 1.0% is found.

Phthalyl content—Transfer about 1 g, accurately weighed, to a conical flask, dissolve in 50 mL of a mixture of alcohol, acetone, and water (2:2:1), add phenolphthalein TS, and titrate with 0.1 *N* sodium hydroxide VS. Perform a blank determination, and make any necessary correction. Calculate the percentage of phthalyl taken by the formula:

$$0.01(149.1)(V/W)– 2(149/166.1)(P),$$

in which 149.1 and 166.1 are the molecular weights of the phthalyl group and phthalic acid, respectively, V is the volume, in mL, of 0.1 *N* sodium hydroxide consumed after correction for the blank, W is the weight, in g, calculated on the anhydrous basis, of Hypromellose Phthalate taken, and P is the percentage of free phthalic acid found as directed in the test for *Limit of free phthalic acid*.

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