Edition: BP 2025 (Ph. Eur. 11.6 update)

Hypromellose[1]

General Notices

(Ph. Eur. monograph 0348)

9004-65-3

Action and use

Artificial tears.

Preparation

Hypromellose Eye Drops

Ph Eur

DEFINITION

Hydroxypropylmethylcellulose. Cellulose, 2-hydroxypropylmethyl ether.

Partly *O*-methylated and *O*-(2-hydroxypropylated) cellulose.

Content

Methoxy ($-OCH_3$; M_r 31.03) and hydroxypropoxy ($-OC_3H_6OH$; M_r 75.09) groups (dried substance) conforming to the types of hypromellose set forth in the accompanying table.

Substitution type	Methoxy (per cent)	Hydroxypropoxy (per cent)
1828	16.5 to 20.0	23.0 to 32.0
2208	19.0 to 24.0	4.0 to 12.0
2906	27.0 to 30.0	4.0 to 7.5
2910	28.0 to 30.0	7.0 to 12.0

♦ CHARACTERS

Appearance

White, yellowish-white or greyish-white powder or granules, hygroscopic after drying.

Solubility

Practically insoluble in hot water, in acetone, in anhydrous ethanol and in toluene. It dissolves in cold water giving a colloidal solution.♦

IDENTIFICATION

A. Evenly distribute 1.0 g onto the surface of 100 mL of *water R* in a beaker, tapping the top of the beaker gently if necessary to ensure a uniform layer on the surface. Allow to stand for 1-2 min: the powdered material aggregates on the surface.
B. Evenly distribute 1.0 g into 100 mL of boiling *water R*, and stir the mixture using a magnetic stirrer with a bar 25 mm long: a slurry is formed and the particles do not dissolve. Allow the slurry to cool to 10 °C and stir using a magnetic stirrer: a clear or slightly turbid solution occurs with its thickness dependent on the viscosity grade.
C. To 0.1 mL of the solution obtained in identification test B add 9 mL of a 90 per cent *V/V* solution of *sulfuric acid R*, shake, heat on a water-bath for exactly 3 min, immediately cool in an ice-bath, carefully add 0.6 mL of a 20 g/L solution of *ninhydrin R*, shake and allow to stand at 25 °C: a red colour develops at first and changes to purple within 100 min.
D. Place 2-3 mL of the solution obtained in identification test B onto a glass slide as a thin film and allow the water to evaporate: a coherent, clear film forms on the glass slide.
E. Add 50.0 mL of the solution obtained in identification test B to 50.0 mL of *water R* in a beaker. Insert a thermometer into the solution. Stir the solution on a magnetic stirrer/hot plate and begin heating, increasing the temperature at a rate of 2-5 °C per minute. Determine the temperature at which a turbidity increase begins to occur and designate the temperature as the flocculation temperature: the flocculation temperature is higher than 50 °C.

TESTS

◊ Appearance of solution

The solution is not more opalescent than reference suspension III (*2.2.1*) and not more intensely coloured than reference solution Y_6 (*2.2.2, Method II*).

While stirring, introduce a quantity of the substance to be examined equivalent to 1.0 g of the dried substance into 50 g of *carbon dioxide-free water R* heated to 90 °C. Allow to cool, adjust the mass of the solution to 100 g with *carbon dioxide-free water R* and stir until dissolution is complete.◊

pH (*2.2.3*)

5.0 to 8.0 for the solution prepared as described under Viscosity.

Read the pH after the probe has been immersed for 5 ± 0.5 min.

Viscosity

80 per cent to 120 per cent of the nominal value for samples with a viscosity less than 600 mPa·s (Method 1); 75 per cent to 140 per cent of the nominal value for samples with a viscosity of 600 mPa·s or higher (Method 2).

Method 1, to be applied to samples with a viscosity of less than 600 mPa·s Weigh a quantity of the substance to be examined equivalent to 4.000 g of the dried substance. Transfer into a wide-mouthed bottle, and adjust the total mass of the sample and the water to 200.0 g with hot *water R* (90-99 °C). Capping the bottle, stir by mechanical means at 400 ± 50 r/min for 10-20 min until the particles are thoroughly dispersed and wetted. Scrape down the insides of the bottle with a spatula if necessary, to ensure that there is no undissolved material on the sides of the bottle, and continue the stirring in a cooling water-bath maintained at a temperature below 10 °C for another 20-40 min. Adjust the solution mass if necessary to 200.0 g using cold *water R*. Centrifuge the solution if necessary to expel any entrapped air bubbles. Using a spatula, remove any foam. Determine the kinematic viscosity (ν) of this solution using the capillary viscometer method (*2.2.9*). Separately determine the density (ρ) (*2.2.5*) of the solution and calculate the dynamic viscosity (η) using the expression $\eta = \rho\nu$.

Method 2, to be applied to samples with a viscosity of 600 mPa·s or higher Weigh a quantity of the substance to be examined equivalent to 10.00 g of the dried substance. Transfer into a wide-mouthed bottle, and adjust the total mass of the sample and the water to 500.0 g with hot *water R* (90-99 °C). Capping the bottle, stir by mechanical means at 400 ± 50 r/min for 10-20 min until the particles are thoroughly dispersed and wetted. Scrape down the insides of the bottle with a spatula if necessary, to ensure that there is no undissolved material on the sides of the bottle, and continue the stirring in a cooling water-bath maintained at a temperature below 10 °C for another 20-40 min. Adjust the solution mass if necessary to 500.0 g using cold *water R*. Centrifuge the solution if necessary to expel any entrapped air bubbles. Using a spatula, remove any foam. Determine the viscosity (*2.2.10*) of this solution at 20 ± 0.1 °C using a rotating viscometer.

Apparatus Single-cylinder type spindle viscometer.

Rotor number, revolution and calculation multiplier Apply the conditions specified in Table 0348.-1.

Table 0348.-1.

Nominal viscosity* (mPa·s)	Rotor number	Revolution (r/min)	Calculation multiplier
600 to less than 1400	3	60	20
1400 to less than 3500	3	12	100
3500 to less than 9500	4	60	100
9500 to less than 99 500	4	6	1000
99 500 or more	4	3	2000

*The nominal viscosity is based on the manufacturer's specifications.

Allow the spindle to rotate for 2 min before taking the measurement. Allow a rest period of at least 2 min between subsequent measurements. Repeat the measurement twice and determine the mean of the 3 readings.

Loss on drying (*2.2.32*)

Maximum 5.0 per cent, determined on 1.000 g by drying in an oven at 105 °C for 1 h.

Sulfated ash (*2.4.14*)

Maximum 1.5 per cent, determined on 1.0 g.

ASSAY

Gas chromatography (*2.2.28*).

Apparatus:

— *reaction vial*: a 5 mL pressure-tight vial equipped with a pressure-tight butyl rubber membrane stopper coated with polytetrafluoroethylene and secured with an aluminium crimp cap or another sealing system providing sufficient air-tightness;

— *heater*: a heating module with a square aluminium block having holes so that the reaction vials fit; mixing of the contents of the vial is effected using a magnetic stirrer equipped in the heating module or using a reciprocal shaker that performs approximately 100 cycles/min.

Internal standard solution To 10 mL of *o-xylene R* add 3.0 mL of *octane R* and dilute to 100.0 mL with *o-xylene R*.

Test solution Weigh 65.0 mg of the substance to be examined, place in a reaction vial, add 0.06-0.10 g of *adipic acid R*, 2.0 mL of the internal standard solution and 2.0 mL of *hydriodic acid R*, immediately cap and seal the vial and weigh accurately. Mix the contents of the vial continuously for 60 min while heating the block so that the temperature of the contents is maintained at 130 ± 2 °C. If a reciprocal shaker or magnetic stirrer cannot be used, shake the vial thoroughly by hand at 5 min intervals during the initial 30 min of the heating time. Allow the vial to cool, and weigh accurately. If the loss of mass is less than 26 mg and there is no evidence of a leak, use the upper layer of the mixture as the test solution.

Reference solution Place 0.06-0.10 g of *adipic acid R*, 2.0 mL of the internal standard solution and 2.0 mL of *hydriodic acid R* in another reaction vial, cap and seal the vial and weigh accurately. Add 15-22 µL of *isopropyl iodide R* through the septum with a syringe, weigh accurately, add 45 µL of *methyl iodide R* in the same manner and weigh accurately. Shake the reaction vial thoroughly and use the upper layer as the reference solution.

Use a precolumn if needed.

Column:

— *material*: fused silica;

— *size*: *l* = 30 m, Ø = 0.53 mm;

— *stationary phase*: *methylpolysiloxane R* (3 µm).

Carrier gas *helium for chromatography R*.

Flow rate 4.3 mL/min.

Split ratio 1:40.

Temperature:

	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

Detection Flame ionisation or thermal conductivity.

Injection 1-2 µL.

Relative retention With reference to octane (retention time = about 10 min): methyl iodide = about 0.4; isopropyl iodide = about 0.7.

System suitability Reference solution:

— *resolution*: minimum 5.0 between the peaks due to methyl iodide and isopropyl iodide and between the peaks due to isopropyl iodide and octane;

— *repeatability*: maximum relative standard deviation of 2.0 per cent for the ratios of the areas of the peaks respectively due to methyl iodide and isopropyl iodide to the area of the peak due to octane, determined on 6 injections.

Calculate the response factor (R) using the following expression:

$$\frac{A_1 \times m_1 \times C}{A_2 \times 100}$$

A_1 = area of the peak due to the internal standard in the chromatogram obtained with the reference solution;

A_2 = area of the peak due to methyl iodide in the chromatogram obtained with the reference solution;

m_1 = mass of *methyl iodide R* in the reference solution, in milligrams;

C = percentage content of *methyl iodide R*.

Calculate the percentage content of methoxy groups using the following expression:

$$\frac{A_4 \times R \times M_1 \times 100}{A_3 \times m_2 \times M_2}$$

A_3 = area of the peak due to the internal standard in the chromatogram obtained with the test solution;

A_4 = area of the peak due to methyl iodide in the chromatogram obtained with the test solution;

R = response factor;

M_1 = molar mass of methoxy group (31.0);

M_2 = molar mass of methyl iodide (141.9);

m_2 = mass of the sample (dried substance) in the test solution, in milligrams.

Calculate the response factor (*R*) using the following expression:

$$\frac{A_1 \times m_1 \times C}{A_2 \times 100}$$

A_1	=	area of the peak due to the internal standard in the chromatogram obtained with the reference solution;
A_2	=	area of the peak due to isopropyl iodide in the chromatogram obtained with the reference solution;
m_1	=	mass of *isopropyl iodide R* in the reference solution, in milligrams;
C	=	percentage content of *isopropyl iodide R*.

Calculate the percentage content of hydroxypropoxy groups using the following expression:

$$\frac{A_4 \times R \times M_1 \times 100}{A_3 \times m_2 \times M_2}$$

A_3	=	area of the peak due to the internal standard in the chromatogram obtained with the test solution;
A_4	=	area of the peak due to isopropyl iodide in the chromatogram obtained with the test solution;
R	=	response factor;
M_1	=	molar mass of hydroxypropoxy group (75.1);
M_2	=	molar mass of isopropyl iodide (170.0);
m_2	=	mass of the sample (dried substance) in the test solution, in milligrams.

LABELLING

The label states:

— the nominal viscosity in millipascal seconds (mPa·s);

— the substitution type.

◊ 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). Some of the characteristics described in the Functionality-related characteristics section may also be present in the mandatory part of the monograph since they also represent mandatory quality criteria. In such cases, a cross-reference to the tests described in the mandatory part is included in the Functionality-related characteristics section. Control of the characteristics can 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 hypromellose used as binder, viscosity-increasing agent or film former.

Viscosity

See Tests.

Degree of substitution

See Assay.

The following characteristics may be relevant for hypromellose used as matrix former in prolonged-release tablets.

Viscosity

See Tests.

Degree of substitution

See Assay.

Molecular mass distribution (*2.2.30*)

Particle-size distribution (*2.9.31* or *2.9.38*)

Powder flow (*2.9.36*).◊

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1 This monograph has undergone pharmacopoeial harmonisation. See chapter *5.8 Pharmacopoeial harmonisation*.