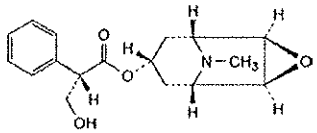
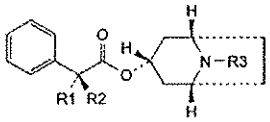
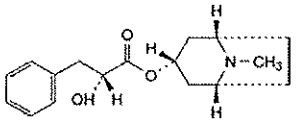


D. (1*R*,2*R*,4*S*,5*S*,7*s*)-9-methyl-3-oxa-9-azatricyclo[3.3.1.0^{2,4}]non-7-yl (2*S*)-3-hydroxy-2-phenylpropanoate (hyoscine),



E. R1 = CH_2OH, R2 = R3 = H: (1*R*,3*r*,5*S*)-8-azabicyclo[3.2.1]oct-3-yl (2*S*)-3-hydroxy-2-phenylpropanoate (norhyoscyamine),

G. R1 + R2 = CH_2, R3 = CH_3: (1*R*,3*r*,5*S*)-8-methyl-8-azabicyclo[3.2.1]oct-3-yl 2-phenylprop-2-enoate (apoatropine),



F. (1*R*,3*r*,5*S*)-8-methyl-8-azabicyclo[3.2.1]oct-3-yl (2*R*)-2-hydroxy-3-phenylpropanoate (littorine).

01/2008:0348
corrected 6.3

HYPROMELLOSE

Hypromellosum

[9004-65-3]

DEFINITION

Hydroxypropylmethylcellulose.

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

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 on 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 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 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 exactly 50 mL of the solution obtained in identification B to exactly 50 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

Solution S. 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.

Appearance of solution. Solution S 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*).

pH (*2.2.3*): 5.0 to 8.0 for the solution prepared as described under Apparent viscosity.

Carry out the test at 20 ± 2 °C and read the indicated pH value after the probe has been immersed for 5 ± 0.5 min.

Heavy metals (*2.4.8*): maximum 20 ppm.

1.0 g complies with test F. Prepare the reference solution using 2 mL of *lead standard solution (10 ppm Pb) R*.

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.

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). This section is a non-mandatory part of the monograph and it is not necessary to verify the characteristics to demonstrate compliance. Control of these characteristics can however 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.

Apparent viscosity: minimum 80 per cent and maximum 120 per cent of the nominal value for samples with a viscosity less than 600 mPa·s (Method 1); minimum 75 per cent and maximum 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 accurately 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 mass to 200.0 g with hot *water R*. 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, if present. Determine the viscosity of this solution using the capillary viscometer method (*2.2.9*) to obtain the kinematic viscosity (ν). Separately, determine the density (ρ) (*2.2.5*) of the solution and calculate the dynamic viscosity (η), as $\eta = \rho\nu$.

Method 2, to be applied to samples with a viscosity of 600 mPa·s or higher. Weigh accurately 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 mass to 500.0 g with hot *water R*. 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, if present. 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.

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

Table 0348.-1.

Labelled 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.

Degree of substitution. Gas chromatography (*2.2.28*).

Apparatus:

- *reaction vial*: a 5 mL pressure-tight vial, 50 mm in height, 20 mm in external diameter and 13 mm in internal diameter at the mouth, equipped with a pressure-tight butyl rubber membrane stopper coated with polytetrafluoroethylene and secured with an aluminium crimped cap or another sealing system providing a sufficient air-tightness;
- *heater*: a heating module with a square aluminium block having holes 20 mm in diameter and 32 mm in depth, 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: 30 g/L solution of *octane R* in *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 well by hand at 5-minute intervals during the initial 30 min of the heating time. Allow the vial to cool, and again weigh accurately. If the loss of mass is less than 0.50 per cent of the contents 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 well, and use the upper layer as the reference solution.

Column:

- *size*: *l* = 1.8-3 m, Ø = 3-4 mm;
- *stationary phase*: *diatomaceous earth for gas chromatography R* impregnated with 10-20 per cent of *poly(dimethyl)(75)(diphenyl)(25)siloxane R* (film thickness 125-150 µm);
- *temperature*: 100 °C.

Carrier gas: *helium for chromatography R* (thermal conductivity); *helium for chromatography R* or *nitrogen for chromatography R* (flame ionisation).

Flow rate: adjusted so that the retention time of the internal standard is about 10 min.

Detection: flame ionisation or thermal conductivity.

Injection: 1-2 µL.

System suitability: reference solution:

- *resolution*: well resolved peaks of methyl iodide (1st peak), isopropyl iodide (2nd peak) and internal standard (3rd peak).

Calculation:

- *methoxy and hydroxypropoxy groups*: calculate the ratios (Q_1 and Q_2) of the areas of the peaks due to methyl iodide and isopropyl iodide to the area of the peak due to the internal standard in the chromatogram obtained with the test solution, and the ratios (Q_3 and Q_4) of the areas of the peaks due to methyl iodide and isopropyl iodide to the area of the peak due to the internal standard in the chromatogram obtained with the reference solution.

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

$$\frac{Q_1}{Q_3} \times \frac{m_1}{m} \times 21.864$$

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

$$\frac{Q_2}{Q_4} \times \frac{m_2}{m} \times 44.17$$

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

m_2 = mass of isopropyl iodide in the reference solution, in milligrams;

m = mass of the sample (dried substance), in milligrams.

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

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

Apparent viscosity: see test above.

Degree of substitution: see test above.

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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corrected 6.3

HYPROMELLOSE PHTHALATE

Hypromellosi phthalas

DEFINITION

Hydroxypropylmethylcellulose phthalate.

Monophthalic acid ester of hypromellose, containing methoxy ($-OCH_3$), 2-hydroxypropoxy ($-OCH_2CHOHCH_3$) and phthaloyl (*o*-carboxybenzoyl $C_8H_5O_3$) groups.

CHARACTERS

Appearance: white or almost white, free-flowing flakes or granular powder.

Solubility: practically insoluble in water, soluble in a mixture of equal volumes of acetone and methanol and in a mixture of equal volumes of methanol and methylene chloride, very slightly soluble in acetone and in toluene, practically insoluble in anhydrous ethanol.

IDENTIFICATION

Infrared absorption spectrophotometry (*2.2.24*).

Preparation: dissolve 40 mg in 1 mL of a mixture of equal volumes of *methanol R* and *methylene chloride R*; spread 2 drops of this solution between 2 sodium chloride plates, then remove one of the plates to evaporate the solvent.

Comparison: *hypromellose phthalate CRS*.

TESTS

Free phthalic acid. Liquid chromatography (*2.2.29*).

Test solution. Dissolve 0.20 g of the substance to be examined in about 50 mL of *acetonitrile R* with the aid of ultrasound. Add 10 mL of *water R*, cool to room temperature, dilute to 100.0 mL with *acetonitrile R* and mix.

Reference solution. Dissolve 12.5 mg of *phthalic acid R* in 125 mL of *acetonitrile R*. Add 25 mL of *water R*, dilute to 250.0 mL with *acetonitrile R* and mix.

Column:

- *size*: *l* = 0.25 m, Ø = 4.6 mm;
- *stationary phase*: *octadecylsilyl silica gel for chromatography R* (5-10 µm).

Mobile phase: *acetonitrile R*, 1 g/L solution of *trifluoroacetic acid R* (1:9 *V/V*).

Flow rate: 2.0 mL/min.

Detection: spectrophotometer at 235 nm.

Injection: 10 µL.

System suitability: reference solution:

- *repeatability*: maximum relative standard deviation of 1.0 per cent after 2 injections.

Limit:

- *phthalic acid*: not more than 0.4 times the area of the corresponding peak in the chromatogram obtained with the reference solution (1.0 per cent).

Chlorides: maximum 0.07 per cent.

Dissolve 1.0 g in 40 mL of *0.2 M sodium hydroxide*, add 0.05 mL of *phenolphthalein solution R* and add *dilute nitric acid R* dropwise, with stirring, until the red colour disappears. Add an additional 20 mL of *dilute nitric acid R* with stirring. Heat on a water-bath with stirring until the gel-like precipitate formed becomes granular. Cool and centrifuge. Separate the liquid phase and wash the residue with 3 quantities, each of 20 mL, of *water R*, separating the washings by centrifugation. Combine the liquid phases, dilute to 200 mL with *water R*, mix and filter. To 50 mL of this solution, add 1 mL of *0.1 M silver nitrate*. The solution is not more opalescent than a standard prepared by mixing 0.5 mL of *0.01 M hydrochloric acid* with 10 mL of *0.2 M sodium hydroxide*, adding 7 mL of *dilute nitric acid R* and 1 mL of *0.1 M silver nitrate*, and diluting to 50 mL with *water R*.

Heavy metals (*2.4.8*): maximum 10 ppm.

2.0 g complies with test C. Prepare the reference solution using 2 mL of *lead standard solution (10 ppm Pb) R*.

Water (*2.5.12*): maximum 5.0 per cent, determined on 0.500 g.

Sulfated ash (*2.4.14*): maximum 0.2 per cent, determined on 1.0 g.

STORAGE

In an airtight container.

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). This section is a non-mandatory part of the monograph and it is not necessary to verify the characteristics to demonstrate compliance. Control of these characteristics can however 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 phthalate used as a gastro-resistant coating agent.

Apparent viscosity (*2.2.9*): 80 per cent to 120 per cent of the nominal value.

Dissolve 10 g, previously dried at 105 °C for 1 h, in 90 g of a mixture of equal masses of *methanol R* and *methylene chloride R* by mixing and shaking.

Solubility. 0.2 g does not dissolve in *0.1 M hydrochloric acid* but dissolves quickly and completely in 100 mL of *phosphate buffer solution pH 6.8 R* with stirring.

Phthaloyl groups: typically 21.0 per cent to 35.0 per cent (anhydrous substance).

Dissolve 1.000 g in 50 mL of a mixture of 1 volume of *water R*, 2 volumes of *acetone R* and 2 volumes of *ethanol (96 per cent) R*. Add 0.1 mL of *phenolphthalein solution R* and titrate with *0.1 M sodium hydroxide* until a faint pink colour is obtained. Carry out a blank titration.

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

$$\frac{149n}{(100-a)\,m} - 1.795S$$

a = percentage content of water;

m = mass of the substance to be examined, in grams;

n = volume of *0.1 M sodium hydroxide* used, in millilitres;

S = percentage content of free phthalic acid (see Tests).

Monographs F-H