Methylphenidate Prolonged-release Capsules

Methylphenidate Prolonged-release Capsules from different manufacturers, whilst complying with the requirements of the monograph, are not interchangeable unless otherwise justified and authorised.

Details for the public consultation of this monograph are as follows:

<table>
<thead>
<tr>
<th>EAG/Panel/Working Party</th>
<th>Medicinal Chemicals 2</th>
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</thead>
</table>
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| Deadline for Comment    | 30th September 2019   |
| Target Publication Date (subject to change) | BP 2021 |
| Notes                   | New monograph  
                          | If limits are too restrictive, please provide batch/stability data to demonstrate that an increase is required. |

Action and use

Narcolepsy; hyperactivity disorder in children.

DEFINITION

Methylphenidate Prolonged-release Capsules contain Methylphenidate Hydrochloride.

PRODUCTION

A suitable dissolution test is carried out to demonstrate the appropriate release of Methylphenidate Hydrochloride. The dissolution profile reflects the in vivo performance which in turn is compatible with the dosage schedule recommended by the manufacturer.

The capsules comply with the requirements stated under Capsules and with the following requirements.

Content of methylphenidate hydrochloride, $\text{C}_{14}\text{H}_{19}\text{N}_{2}\text{HCl}$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

Shake a quantity of mixed capsule contents containing 50 mg of Methylphenidate Hydrochloride with 20 mL of dichloromethane, centrifuge and filter. Evaporate the filtrate to about 5 mL and add ether slowly until crystals form. Filter, wash the crystals with ether and dry at 80° for 30 minutes. The infrared absorption spectrum of the residue, Appendix II A, is concordant with the reference spectrum of methylphenidate hydrochloride (RS 485).
TESTS

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

4 volumes of methanol and 11 volumes of a solution of 0.273% w/v of *potassium dihydrogen phosphate*, adjusted to pH 4.0 with *glacial acetic acid* (solution A).

(1) To a quantity of the mixed capsule contents containing 60 mg of Methylphenidate Hydrochloride, add 20 mL of acetone and mix with the aid of ultrasound for about 15 minutes. Add 100 mL of solution A and shake vigorously on a mechanically shaker for at least 30 minutes. Dilute to 250 mL with solution A, filter through a 0.45-µm PTFE filter and use the filtrate.

(2) Dilute 1 volume of solution (1) to 200 volumes with solution A.

(3) 0.002% w/v of *methylphenidate impurity mixture EPCRS* and 0.0001% w/v of *methylphenidate impurity C EPCRS* in solution A.

(4) Dilute 1 volume of solution (2) to 5 volumes with solution A.

CHROMATOGRAPHIC CONDITIONS

(a) A stainless steel column (7.5 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (3.5 µm) (Symmetry C18 is suitable).

(b) Use gradient elution and the mobile phase described below.

(c) Use a flow rate of 1.3 mL per minute.

(d) Use a column temperature of 40°C.

(e) Use a detection wavelength of 215 nm.

(f) Inject 100 µL of each solution.

MOBILE PHASE

*Mobile phase A* Dissolve 2.16 g of *sodium octanesulfonate* in 950 mL of water, add 1.0 mL of *triethylamine*, adjust to pH 2.7 with *orthophosphoric acid* and dilute to 1000 mL with water.

*Mobile phase B* acetonitrile R1.

<table>
<thead>
<tr>
<th>Time (Minutes)</th>
<th>Mobile phase A (% v/v)</th>
<th>Mobile phase B (% v/v)</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-15</td>
<td>80</td>
<td>20</td>
<td>isocratic</td>
</tr>
<tr>
<td>15-35</td>
<td>80→60</td>
<td>20→40</td>
<td>linear gradient</td>
</tr>
<tr>
<td>35-36</td>
<td>60→80</td>
<td>40→20</td>
<td>linear gradient</td>
</tr>
<tr>
<td>36-45</td>
<td>80</td>
<td>20</td>
<td>re-equilibration</td>
</tr>
</tbody>
</table>

When the chromatograms are recorded under the prescribed conditions, the relative retentions with reference to methylphenidate (retention time about 20 minutes) are: impurity A, about 0.35; impurity C, about 0.4 and impurity B, about 0.6.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to impurity A and impurity C is at least 1.5.
LIMITS

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity A is not greater than 3 times the area of the principal peak in the chromatogram obtained with solution (2) (1.5%);

the area of any peak corresponding to impurity B is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.5%);

the area of any other secondary peak is not greater than 0.4 times the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);

the sum of the areas of any secondary peaks is not greater than 4 times the area of the principal peak in the chromatogram obtained with solution (2) (2.0%).

Disregard any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (4) (0.1%).

ASSAY

Weigh the contents of 20 capsules. Mix, and powder if necessary. Carry out the method for liquid chromatography, Appendix III D, using the following solutions.

4 volumes of methanol and 11 volumes of a solution of 0.273% w/v of potassium dihydrogen phosphate, adjusted to pH 4.0 with glacial acetic acid (solution A).

(1) To a quantity of the mixed capsule contents containing 60 mg of Methylphenidate Hydrochloride, add 20 mL of acetone and mix with the aid of ultrasound for about 15 minutes. Add 100 mL of solution A and shake vigorously on a mechanically shaker for at least 30 minutes. Dilute to 250 mL with solution A and filter through a 0.45-µm PTFE filter. Dilute 2 volumes of the filtrate to 5 volumes with the mobile phase.

(2) 0.0096% w/v of methylphenidate hydrochloride BPCRS in the mobile phase.

(3) 0.015% w/v each of methylphenidate hydrochloride BPCRS and phenylephrine hydrochloride BPCRS in the mobile phase.

CHROMATOGRAPHIC CONDITIONS

(a) A stainless steel column (25 cm × 4.6 mm) packed with cyanosilyl silica gel for chromatography (5 µm) (Spherosorb CN is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 1.5 mL per minute.
(d) Use an ambient column temperature.
(e) Use a detection wavelength of 210 nm.
(f) Inject 10 µL of each solution.

MOBILE PHASE

300 volumes of a 0.16% w/v solution of anhydrous sodium acetate pH adjusted to 4.0 with glacial acetic acid, 300 volumes of acetonitrile R1 and 400 volumes of methanol.

When the chromatograms are recorded under the prescribed conditions the retention time of methylphenidate is about 4 minutes.
SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the resolution between the peaks due to phenylephrine and methylphenidate is not less than 2.0.

DETERMINATION OF CONTENT

Calculate the content of C_{14}H_{19}NO_{2},HCl, in the capsules using the declared content of C_{14}H_{19}NO_{2},HCl in *methylphenidate hydrochloride BPCRS*.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under *Methylphenidate Hydrochloride*.