### Methylphenidate Prolonged-release Tablets

*Methylphenidate Prolonged-release Tablets* 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>
</tr>
</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 Tablets* 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 tablets comply with the requirements stated under Tablets and with the following requirements.*

**Content of methylphenidate hydrochloride, C₁₄H₁₉N₂O₂.HCl**

95.0 to 105.0% of the stated amount.

**IDENTIFICATION**

A. Carry out the method for thin-layer chromatography, Appendix III A, using the following solutions.

1. Stir a quantity of crushed tablets containing 50 mg of Methylphenidate Hydrochloride with 20 mL of dichloromethane and filter through a PTFE filter. Evaporate the filtrate to dryness and reconstitute in 5 mL of methanol. Filter through a PTFE syringe filter and use the filtrate.
(2) 0.1% w/v of methylphenidate hydrochloride BPCRS in methanol.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating silica gel F254 (Merck silica gel 60 F254 plates are suitable).
(b) Use the mobile phase as described below.
(c) Apply 20 µL of each solution.
(d) Develop the plate to 15 cm.
(e) After removal of the plate allow it to dry in air and spray with potassium iodobismuthate R2 solution.

MOBILE PHASE

3 volumes of 18 M ammonia, 7 volumes of methanol and 9 volumes of ethyl acetate.

CONFIRMATION

The principal spot in the chromatogram obtained with solution (1) is similar in position and colour to that in the chromatogram obtained with solution (2).

B. In the Assay, the retention time of the principal peak in the chromatogram obtained with solution (1) is similar to that of the peak in the chromatogram obtained with solution (2).

TESTS

Related substances

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

A mixture of equal volumes of acetonitrile R1 and methanol (solution A).

Water adjusted to pH 3.0 with orthophosphoric acid (solution B).

(1) To a number of whole tablets containing 108 mg of Methylphenidate Hydrochloride, add 100 mL of solution A and stir on a magnetic stirrer for at least 4 hours. Add 300 mL of solution B, stir for at least 30 minutes and dilute to 500 mL with solution C. Centrifuge a portion of the solution and use the supernatant liquid.

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

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

(4) Dilute 1 volume of solution (2) to 5 volumes with mobile phase 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°.
(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 twice the area of the principal peak in the chromatogram obtained with solution (2) (1.0%);
- 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

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

Dissolve 5.93 g of ammonium dihydrogen phosphate and 1.68 g of sodium octanesulfonate in 1000 mL of water, add 1.0 mL of triethylamine and adjust to pH 3.1 with orthophosphoric acid (solution A).

(1) To 10 whole tablets, add 50 mL of solution A and shake. Add 100 mL of acetonitrile R1 and shake mechanically for about 2 hours. Add a further 300 mL of solution A and shake for about 1 hour. Dilute to 500 mL with solution A. Centrifuge a portion of the solution and dilute the supernatant liquid with sufficient solution A to produce a solution containing 0.009% w/v of Methylphenidate Hydrochloride.
(2) 0.009% 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) (Spherisorb 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 C₁₄H₁₉NO₂.HCl, in the tablets using the declared content of C₁₄H₁₉NO₂.HCl in methylphenidate hydrochloride BPCRS.

IMPURITIES

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