Methadone Tablets

General Notices

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

<table>
<thead>
<tr>
<th>EAG MC3</th>
<th>Medicinal Chemicals 3</th>
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<tbody>
<tr>
<td><strong>Contact Details</strong></td>
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<tr>
<td><strong>Deadline for Comment</strong></td>
<td>30th June 2020</td>
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<tr>
<td><strong>Target Publication Date (subject to change)</strong></td>
<td>BP 2022</td>
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<td><strong>Notes:</strong></td>
<td>Revised monograph</td>
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Action and use

Opioid receptor agonist; analgesic.

**DEFINITION**

Methadone Tablets contain Methadone Hydrochloride.

*The tablets comply with the requirements stated under Tablets and with the following requirements.*

Content of methadone hydrochloride, C_{21}H_{27}NO,HCl

92.5 to 107.5% of the stated amount.

**IDENTIFICATION**

Shake a quantity of the powdered tablets containing 0.1 g of Methadone Hydrochloride with 20 mL of *water* and centrifuge. Make the supernatant liquid alkaline with 5M *sodium hydroxide*, stir with a glass rod until the precipitate solidifies, filter, wash with *water* and dry over *phosphorus pentoxide* at room temperature at a pressure of 2 kPa. The *infrared absorption spectrum* of the residue, Appendix II A, is concordant with the *reference spectrum* of methadone *(RS 218).*

**TESTS**
Dissolution

Comply with the dissolution test for tablets and capsules, Appendix XII B1.

TEST CONDITIONS

(a) Use Apparatus 2, rotating the paddle at 75 revolutions per minute.
(b) Use 500 mL of water, at a temperature of 37°, as the medium.

PROCEDURE

(1) After 45 minutes withdraw a sample of the medium and filter. measure the absorbance of the filtered sample, suitably diluted with the dissolution medium if necessary, at the maximum at 220 nm, Appendix II B, using water in the reference cell.
(2) Measure the absorbance of a 0.001% w/v solution of methadone hydrochloride BPCRS in water using water in the reference cell.

DETERMINATION OF CONTENT

Calculate the total content of methadone hydrochloride, C_{21}H_{27}NO,HCl, in the medium from the absorbances obtained and using the declared content of C_{21}H_{27}NO,HCl, in methadone hydrochloride BPCRS.

LIMITS

The amount of methadone hydrochloride released is not less than 80% (Q) of the stated amount.

Related substances

Carry out the method for gas chromatography, Appendix III B, using the following solutions.

(1) To a quantity of powdered tablets containing 10 mg of methadone hydrochloride add 7 mL of methanol and mix with the aid of ultrasound. Dilute to 10 mL with methanol and filter.
(2) Dilute 1 volume of solution (1) to 100 volumes with methanol, further dilute 1 volume of this solution to 5 volumes with methanol.
(3) 0.005% w/v each of imipramine hydrochloride BPCRS and cyclobenzaprine hydrochloride BPCRS in methanol.

CHROMATOGRAPHIC CONDITIONS

(a) Use a (5%-phenyl)-methylpolysiloxane nonpolar column (50 m x 0.32 mm) (1.05 µm) (Agilent HP-5 is suitable).
(b) Use helium as the carrier gas.
(c) Use a flow rate of 1.2 mL per minute.
(d) Use an inlet temperature of 200°, detector temperature of 250° and the column oven temperature described below.
(e) Use a flame ionisation detector.
(f) Inject 2 µL of each solution.
(g) Use a split ratio of 1:10
<table>
<thead>
<tr>
<th>Time (Minutes)</th>
<th>Temperature (°C)</th>
<th>Comment</th>
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<tbody>
<tr>
<td>0-4</td>
<td>150→250</td>
<td>linear gradient</td>
</tr>
<tr>
<td>4-35</td>
<td>250</td>
<td>isothermal</td>
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When the chromatograms are recorded under the prescribed conditions, the relative retentions with reference to methadone hydrochloride (retention time, about 23 minutes) are: imipramine, about 1.2 and cyclobenzaprine, about 1.25.

**SYSTEM SUITABILITY**

The test is not valid unless:

- in the chromatogram obtained with solution (3), the *resolution* between the peaks due to imipramine and cyclobenzaprine is at least 3.0.

- in the chromatogram obtained with solution (2), the *signal-to-noise ratio* of the principal peak is at least 20.

**LIMITS**

In the chromatogram obtained with solution (1):

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

- the sum of the areas of all *secondary peaks* is not greater than 2.5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.5%).

Disregard any peak with an area less than half the area of the principal peak in the chromatogram obtained with solution (2) (0.1%).

**ASSAY**

Weigh and powder 20 tablets. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

1. To a quantity of powdered tablets containing 10 mg of methadone hydrochloride add 75 mL of the mobile phase, mix with the aid of ultrasound, dilute to 100 mL with the same solvent and filter.

2. 0.01% w/v of methadone hydrochloride BPCRS in the mobile phase.

3. 0.01% w/v each of methadone hydrochloride BPCRS and imipramine BPCRS in the mobile phase.

**CHROMATOGRAPHIC CONDITIONS**

1. Use a stainless steel column 25 cm × 4.6mm packed with octadecylsilyl silica gel for chromatography (10 µm) (Phenomenex Bondclone C18 is suitable).
2. Use isocratic elution and the mobile phase described below.
3. Use a flow rate of 1.5 mL per minute.
(d) Use an ambient column temperature.
(e) Use a detection wavelength of 220 nm.
(f) Inject 20 µL of each solution.

MOBILE PHASE

50 volumes of a 0.02M solution of potassium dihydrogen orthophosphate and 50 volumes of acetonitrile, adjust the pH of the final solution pH 5.5 with 2M sodium hydroxide.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the resolution between imipramine and methadone hydrochloride is at least 1.5.

DETERMINATION OF CONTENT

Calculate the content of methadone hydrochloride, C21H27NO,HCl, in the tablets from the chromatograms obtained and using the declared content of C21H27NO,HCl, in methadone hydrochloride BPCRS.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under methadone hydrochloride.