General Notices

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>
<tbody>
<tr>
<td>Contact Details</td>
<td><a href="mailto:helen.corns@mhra.gov.uk">helen.corns@mhra.gov.uk</a></td>
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<tr>
<td>Deadline for Comment</td>
<td>30th December 2020</td>
</tr>
<tr>
<td>Target Publication Date (subject to change)</td>
<td>BP 2022</td>
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<tr>
<td>Notes</td>
<td>Revised monograph</td>
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<tr>
<td></td>
<td>If limits are too restrictive, please provide batch/stability data to demonstrate that an increase is required.</td>
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<tr>
<td></td>
<td>Related substances Chromatographic conditions revised to improve chromatography</td>
</tr>
</tbody>
</table>

Action and use

Cyclo-oxygenase inhibitor; analgesic; anti-inflammatory.

DEFINITION

Ibuprofen Gel is a solution of Ibuprofen in a suitable water-miscible basis.

The gel complies with the requirements stated under Topical Semi-solid Preparations and with the following requirements.

Content of ibuprofen, C₁₃H₁₈O₂

95.0 to 105.0% of the stated amount.

IDENTIFICATION

Disperse a quantity of the gel containing 0.5 g of Ibuprofen with 20 mL of methanol and prepare a solid phase extraction cartridge containing a silica sorbent (Discovery DSC-18 SPE cartridges are suitable) by passing through 2 mL of methanol and 3 mL of water. Mix 1 mL of the sample solution with 1.5 mL of acetic acid (2%) to produce a solution of pH 3.0. Pass the resulting solution through the cartridge, wash the cartridge with 1 mL of a 2% w/v solution of acetic acid and discard the eluent. Pass three 1-mL aliquots of methanol, collect the eluent and evaporate to dryness. The infrared absorption spectrum of the residue, Appendix II A, is concordant with the reference spectrum of ibuprofen (RS 186).

TESTS

file:///H:/Temp/Ibuprofen_Gel_00868BP-Preview.html
Acidity or Alkalinity

pH, 5.5 to 7.5, Appendix V L

Related substances

Carry out the method for liquid chromatography, Appendix III D, using the following solutions prepared in mobile phase A.

(1) Disperse with the aid of ultrasound a quantity of the gel containing 0.2 g of Ibuprofen in 50 mL of mobile phase A, dilute to 100 mL, and filter (Whatman GF/C filter is suitable).

(2) Dilute 1 volume of solution (1) to 100 volumes.

(3) Dissolve 20 mg of ibuprofen BPCRS in 2 mL of acetonitrile R1, add 1 mL of a 0.006% w/v solution of ibuprofen impurity B BPCRS in acetonitrile R1, and dilute to 10 mL.

(4) 0.0006% w/v of 4'-isobutylacetophenone BPCRS (impurity E).

(5) Dissolve the contents of a vial of ibuprofen for peak identification EPCRS (containing impurities A, J, and N) in 1 mL of acetonitrile R1 and dilute to 5 mL.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 4.6 mm) packed with end-capped octadecylsilil amorphous organosilica polymer for chromatography (5 µm) (XTerra MS C18 is suitable).

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

(c) Use a flow rate of 2 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 214 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

Mobile phase A 0.5 volume of orthophosphoric acid, 340 volumes of acetonitrile R1 and sufficient water to produce 1000 volumes

Mobile phase B 0.5 volumes of orthophosphoric acid, 100 volumes of water and 900 volumes of 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>0-25</td>
<td>100</td>
<td>0</td>
<td>isocratic</td>
</tr>
<tr>
<td>25-55</td>
<td>100→0</td>
<td>0→100</td>
<td>linear gradient</td>
</tr>
<tr>
<td>55-70</td>
<td>0</td>
<td>100</td>
<td>isocratic</td>
</tr>
<tr>
<td>70-71</td>
<td>0→100</td>
<td>100→0</td>
<td>linear gradient</td>
</tr>
<tr>
<td>71-85</td>
<td>100</td>
<td>0</td>
<td>re-equilibration</td>
</tr>
</tbody>
</table>

When chromatograms are recorded under the prescribed conditions, the relative retentions with reference to ibuprofen (retention time about 26 minutes) are: impurity J, about 0.2; impurity N, about 0.3; impurity A, about 0.9; impurity B, about 1.08 and impurity E, about 1.11.

SYSTEM SUITABILITY
The test is not valid unless, in the chromatogram obtained with solution (3), the peak-to-valley ratio is at least 5.0, where \( H_p \) is the height above the baseline of the peak due to impurity B and \( H_v \) is the height above the baseline of the lowest point of the curve separating this peak from the peak due to ibuprofen.

**LIMITS**

Use the chromatogram supplied with ibuprofen for peak identification EPCRS and the chromatogram obtained with solution (5) to identify the peaks due to impurities A, J, and N, and the chromatogram obtained with solution (4) to identify the peak due to impurity E.

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity A, J or N, is not greater than 1.5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.15% of each);

the area of any peak corresponding to ibuprofen impurity E is not greater than 3 times the area of the principal peak in the chromatogram obtained with solution (2) (0.3%);

the area of any other secondary peak is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.1%);

the sum of the area of any secondary peaks is not greater than 7 times the area of the principal peak in the chromatogram obtained with solution (2) (0.7%).

Disregard any peak with an area less than 0.5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.05%).

**ASSAY**

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

(1) Disperse with the aid of ultrasound a weighed quantity of the gel containing 50 mg of ibuprofen in 50 mL of methanol, dilute to 100 mL with methanol, and filter (Whatman GF/C filter is suitable). Dilute 1 volume to 2 volumes with the mobile phase.

(2) 0.05% w/v of ibuprofen BPCRS in methanol. Dilute 1 volume to 2 volumes with the mobile phase.

**CHROMATOGRAPHIC CONDITIONS**

(a) Use a stainless steel column (25 cm x 4.6 mm) packed with end-capped octadecysilyl silica gel for chromatography (10 µm) (Nucleosil C18 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 264 nm.

(f) Inject 20 µL of each solution.

**MOBILE PHASE**

3 volumes of orthophosphoric acid, 247 volumes of water and 750 volumes of methanol.

**DETERMINATION OF CONTENT**

Calculate the content of \( C_{13}H_{18}O_2 \) in the gel using the declared content of \( C_{13}H_{18}O_2 \) in ibuprofen BPCRS.
IMPURITIES

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