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Paracetamol, Codeine Phosphate and Caffeine Tablets

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 1</th>
</tr>
</thead>
<tbody>
<tr>
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<tr>
<td>Deadline for Comment</td>
<td>30 September 2020</td>
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<tr>
<td>Target Publication Date (subject to change)</td>
<td>BP 2022</td>
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Notes

Revised monograph
If limits are too restrictive, please provide batch/stability data to demonstrate that an increase is required.

Identification D: colour change test replaced with TLC method
Identification E: additional caffeine identification test added
Dissolution: revised limit
4-aminophenol: test removed
Related substances TLC method revised with HPLC
Assay Revised to accommodate all product strengths

Action and use

Analgesic; antipyretic; opioid receptor agonist.

DEFINITION

Paracetamol, Codeine Phosphate and Caffeine Tablets contain Codeine Phosphate, Paracetamol and Caffeine.

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

Content of paracetamol, C₈H₉NO₂

95.0 to 105.0% of the stated amount.

Content of codeine phosphate, C₁₈H₂₁NO₃,H₃PO₄,½H₂O

95.0 to 105.0% of the stated amount.

Content of caffeine, C₈H₁₀N₄O₂

95.0 to 105.0% of the stated amount.
IDENTIFICATION

A. Shake a quantity of the powdered tablets containing 0.5 g of Paracetamol with 20 mL of acetone, filter and evaporate the filtrate to dryness. The infrared absorption spectrum of the residue, Appendix II A, is concordant with the reference spectrum of paracetamol (RS 258).

B. Carry out the method for thin-layer chromatography, Appendix III A, using the following solutions.
   (1) Shake a quantity of the powdered tablets containing 24 mg of Codeine Phosphate with 30 mL of water for 1 minute and centrifuge. Decant, add 10 mL of 1m sodium hydroxide and 30 mL of dichloromethane to the supernatant liquid, shake for 1 minute and filter the dichloromethane layer through glass-fibre paper (Whatman GF/C is suitable).
   (2) 0.08% w/v of codeine phosphate BPCRS in methanol (50%).
   (3) 0.08% w/v each of codeine phosphate BPCRS and dihydrocodeine tartrate BPCRS in methanol (50%).

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating silica gel F254.
(b) Use the mobile phase described below.
(c) Apply 10 µL of each solution.
(d) Remove the plate, dry in air, spray with ethanolic iron(III) chloride solution and heat at 105° for 10 minutes and examine in daylight.

MOBILE PHASE

1 volume of 13.5m ammonia, 10 volumes of methanol and 90 volumes of dichloromethane.

SYSTEM SUITABILITY

The test is not valid unless the chromatogram obtained with solution (3) shows two clearly separated spots of different colours.

CONFIRMATION

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

C. In the Assay for codeine phosphate, the chromatogram obtained with solution (1) shows a peak with the same retention time as the principal peak in the chromatogram obtained with solution (2).

D. Carry out the method for thin-layer chromatography, Appendix III A, using the following solutions.
   (1) Mix with the aid of ultrasound a quantity of powdered tablets containing 65 mg of caffeine in 10 mL of methanol, and filter (a 0.2-µm nylon filter is suitable).
   (2) 0.65% w/v of caffeine BPCRS in methanol.
   (3) 0.65% w/v of caffeine BPCRS and 5% w/v of paracetamol 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 1 µL of each solution.
(d) Develop the plate to 15 cm.
(e) After removal of the plate, allow it to dry in air, and examine under ultraviolet light (254 nm).

MOBILE PHASE

5 volumes of acetic acid, 5 volumes of ethanol, 5 volumes of water and 50 volumes of ethyl acetate.

SYSTEM SUITABILITY

The test is not valid unless the chromatogram obtained with solution (3) shows two clearly separated spots.
CONFIRMATION

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

E. In the Assay for caffeine, the chromatogram obtained with solution (1) shows a principal peak with the same retention time as the principal peak in the chromatogram obtained with solution (2).

TESTS

Dissolution

Comply with the requirements for Monographs of the British Pharmacopoeia in the dissolution test for tablets and capsules, Appendix XII B1.

TEST CONDITIONS

(a) Use Apparatus 2 and rotate the paddle at 50 revolutions per minute.
(b) Use as the medium 900 mL of a phosphate buffer (pH 5.8), at a temperature of 37°, prepared in the following manner. Mix 250 mL of 0.2 M potassium dihydrogen phosphate and 18.6 mL of 0.2 M sodium hydroxide, and dilute to 1000 mL with water.

PROCEDURE

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

(1) After 45 minutes, withdraw a sample of the medium and filter. Use the filtered dissolution medium, diluted with the mobile phase, if necessary, to produce a solution expected to contain 0.005% w/v of Paracetamol.
(2) 0.005% w/v solution of paracetamol BPCRS in the dissolution medium.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (10 cm × 4.6 mm) packed with octadecylsilyl silica gel for chromatography (5 μm) (Nucleosil C18 is suitable).
(b) Use isocratic elution using the mobile phase described below.
(c) Use a flow rate of 1.5 mL per minute.
(d) Use ambient column temperature.
(e) Use a detection wavelength of 243 nm.
(f) Inject 20 μL of each solution.

MOBILE PHASE

0.01m sodium pentanesulfonate in a mixture of 22 volumes of methanol and 78 volumes of water, the pH of the solution being adjusted to 2.8 using 2m hydrochloric acid.

DETERMINATION OF CONTENT

Calculate the content of C₈H₉NO₂ in the medium using the declared content of C₈H₉NO₂ in paracetamol BPCRS.

LIMITS

The amount of paracetamol released is not less than 75% (Q) of the stated amount.
Related substances

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

Solution A: 0.23% w/v solution of sodium chloride in 30 volumes of mobile phase B and 70 volumes of mobile phase A.

1. Shake with the aid of ultrasound a quantity of the powdered tablets containing 0.5 g of Paracetamol with 50 mL and filter (Chromafil RC 45/25 is suitable).
2. Dilute 1 volume of solution (1) to 100 volumes.
3. 0.0005% w/v of codeine phosphate BPCS and 0.0001% w/v of 4′-chloroacetanilide (paracetamol impurity J).
4. 0.0001% w/v of 4-aminophenol (paracetamol impurity K).
5. 0.00001% w/v of 4′-chloroacetanilide (paracetamol impurity J).
6. 0.01% w/v of methyl codeine (codeine impurity A).
7. Dilute 1 volume of solution (2) to 10 volumes.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 4.6 mm) packed with end-capped octadecylsilyl silica gel for chromatography (2.6 µm) (Kinetex C18 100A is suitable).
(b) Use gradient elution and the mobile phase described below.
(c) Use a flow rate of 0.8 mL per minute.
(d) Use a column temperature of 35°.
(e) Use detection wavelengths of 212 nm and 246 nm.
(f) Inject 20 µL of each solution.

MOBILE PHASE

Mobile phase A 5 mM sodium octanesulfonate, adjusted to pH 2.2 with orthophosphoric acid.

Mobile phase B methanol 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>
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<td>0-2.5</td>
<td>80→70</td>
<td>20→30</td>
<td>linear gradient</td>
</tr>
<tr>
<td>2.5-20</td>
<td>70</td>
<td>30</td>
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<tr>
<td>32-37</td>
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<td>20</td>
<td>re-equilibration</td>
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</table>

When the chromatograms are recorded under the prescribed conditions, the relative retentions with reference to paracetamol (retention time about 3.3 minutes) are: caffeine impurity B, about 0.6; caffeine impurity D, about 0.97; caffeine impurity F, about 1.2; caffeine impurity A, about 1.3; caffeine, about 1.6; paracetamol impurity K, about 2.3; caffeine impurity E, about 2.5; codeine impurity B, about 2.9; codeine, about 4.8; paracetamol impurity J, about 6.1; codeine impurity A, about 8.0, and codeine impurity C, about 8.5.

SYSTEM SUITABILITY

The test is not valid unless:

in the chromatogram obtained with solution (3) at 246 nm, the resolution between the peaks due to codeine and paracetamol impurity J is at least 2.2.
in the chromatogram obtained with solution (4) at 212 nm, the *signal-to-noise ratio* of the peak due to paracetamol impurity K is at least 10.

in the chromatogram obtained with solution (5) at 246 nm, the *signal-to-noise ratio* of the peak due to paracetamol impurity J is at least 10.

**LIMITS**

*For paracetamol impurity J at 246 nm*

In the chromatogram obtained with solution (1):

the area of any peak corresponding to paracetamol impurity J is not greater than the area of the principal peak in the chromatogram obtained with solution (5) (0.001%).

*For all other impurities at 212 nm*

Identify any peaks due to caffeine impurity B, D, and E, and multiply the peak areas by a correction factor of 2.9, 1.3, and 3.3, respectively.

In the chromatogram obtained with solution (1):

the area of any peak corresponding to codeine impurity A is not greater than the area of the corresponding peak in the chromatogram obtained with solution (6) (1%);

the area of any peak corresponding to paracetamol impurity K is not greater than the area of the corresponding peak in the chromatogram obtained with solution (4) (0.01%);

the area of any other *secondary peak* with a relative retention of 2.7 or less (with reference to paracetamol) is not greater than the area of the peak due to paracetamol in the chromatogram obtained with solution (7) (0.1%);

the area of any other *secondary peak* with a relative retention greater than 2.7 (with reference to paracetamol) is not greater than twice the area of the peak due to codeine in the chromatogram obtained with solution (7) (0.2%);

The total impurity content, excluding codeine impurity A, is not greater than 0.75%.

Disregard any peak with an area less than half the area of the peak due to paracetamol in the chromatogram obtained with solution (7) (0.05%)

**Uniformity of content**

Tablets containing less than 2 mg and/or less than 2% w/w of Codeine Phosphate comply with the requirements stated under Tablets, with respect to the content of Codeine Phosphate, using the following method of analysis.

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

(1) Add 100 mL of the mobile phase to one tablet and mix with the aid of ultrasound until completely dispersed. Shake for 10 minutes, dilute to 200 mL with the mobile phase, filter through a glass-fibre filter (Whatman GF/C is suitable) and use the filtrate.

(2) 0.004% w/v of *codeine phosphate BPCRS* in the mobile phase.

**CHROMATOGRAPHIC CONDITIONS**

The chromatographic conditions described under Dissolution may be used but with a detection wavelength of 220 nm.
DETERMINATION OF CONTENT

Calculate the content of C_{18}H_{21}NO_3.H_3PO_4.\frac{1}{2}H_2O in each tablet using the declared content of C_{18}H_{21}NO_3.H_3PO_4.\frac{1}{2}H_2O in codeine phosphate BPCRS.

ASSAY

For paracetamol

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

1. Shake a quantity of the powdered tablets containing 0.5 g of Paracetamol with 100 mL of the mobile phase for 10 minutes, dilute to 200 mL with the same solvent, filter through a glass-fibre filter (Whatman GF/C is suitable) and dilute 5 mL of the filtrate to 250 mL with the mobile phase.
2. 0.005% w/v of paracetamol BPCRS in the mobile phase.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Dissolution may be used.

DETERMINATION OF CONTENT

Calculate the content of C_8H_9NO_2 using the declared content of C_8H_9NO_2 in paracetamol BPCRS.

For codeine phosphate

For tablets containing the equivalent of less than 2 mg and/or less than 2% w/w of codeine phosphate

Use the average of the individual results determined in the test for Uniformity of content.

For tablets containing the equivalent of 2 mg or more and/or 2% w/w or more than of codeine phosphate

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

1. Shake a quantity of the powdered tablets containing 8 mg of Codeine Phosphate with 100 mL of the mobile phase for 10 minutes, dilute to 200 mL with the same solvent, filter through a glass-fibre filter (Whatman GF/C is suitable) and use the filtrate.
2. 0.004% w/v of codeine phosphate BPCRS in the mobile phase.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Dissolution may be used but with a detection wavelength of 220 nm.

DETERMINATION OF CONTENT

Calculate the content of C_{18}H_{21}NO_3.H_3PO_4.\frac{1}{2}H_2O using the declared content of C_{18}H_{21}NO_3.H_3PO_4.\frac{1}{2}H_2O in codeine phosphate BPCRS.

For caffeine

Weigh and powder 20 tablets. Carry out the method for liquid chromatography, Appendix III D, using the following solutions.
(1) Shake a quantity of the powdered tablets containing 30 mg of Caffeine with 100 mL of the mobile phase for 10 minutes, filter through a glass-fibre filter (Whatman GF/C is suitable) and dilute 5 mL of the filtrate to 50 mL with the mobile phase.

(2) 0.003% w/v of caffeine BPCRS in the mobile phase.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Dissolution may be used but with a detection wavelength of 220 nm.

DETERMINATION OF CONTENT

Calculate the content of C₈H₁₀N₄O₂ in each tablet using the declared content of C₈H₁₀N₄O₂ in caffeine BPCRS.

IMPURITIES

The impurities limited by the requirements of this monograph include impurities J and K listed under Paracetamol, impurities A, B, C, I and J listed under Codeine Phosphate, and impurities A, B, D, E, and F listed under Caffeine.