Edition: BP 2025 (Ph. Eur. 11.6 update)

Paracetamol, Codeine Phosphate and Caffeine Tablets

General Notices

Action and use

Analgesic; antipyretic; opioid receptor agonist; central nervous system stimulant.

DEFINITION

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

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

Content of paracetamol, $C_8H_9NO_2$

95.0 to 105.0% of the stated amount.

Content of codeine phosphate, $C_{18}H_{21}NO_3,H_3PO_4,½H_2O$

95.0 to 105.0% of the stated amount.

Content of caffeine, $C_8H_{10}N_4O_2$

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* and centrifuge. Decant, add 10 mL of 1M *sodium hydroxide* and 30 mL of *dichloromethane* to the supernatant liquid, shake 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 F_{254}*.
(b) Use the mobile phase described below.
(c) Apply 10 µL of each solution.
(d) Develop the plate to 15 cm.
(e) After removal of 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* F_{254} (Merck silica gel 60 F_{254} 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 spot corresponding to caffeine in the chromatogram obtained with solution (1) corresponds in position to the principal spot in the chromatogram obtained with solution (2).

E. In the Assay for caffeine, 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).

TESTS

Dissolution

Comply with the *dissolution test for tablets and capsules*, Appendix XII B1, using the following conditions.

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 *0.2M potassium dihydrogen orthophosphate* and 18 mL of *0.2M 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 0.0056% w/v of Paracetamol.
(2) 0.0056% w/v 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 and the mobile phase as 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 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*, adjusted to pH 2.8 using 2M *hydrochloric acid*.

When the chromatograms are recorded under the prescribed conditions the retention time of paracetamol is about 3 minutes.

DETERMINATION OF CONTENT

Calculate the total content of paracetamol, $C_8H_9NO_2$, in the medium using the declared content of $C_8H_9NO_2$ 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 of *sodium chloride* in a mixture of 30 volumes of mobile phase B and 70 volumes of mobile phase A.

(1) Mix 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 BPCRS* 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 *methylcodeine* (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 as 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*.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-2.5	80→70	20→30	linear gradient
2.5-20	70	30	isocratic
20-30	70→20	30→80	linear gradient
30-32	20→80	80→20	linear gradient
32-37	80	20	re-equilibration

When the chromatograms are recorded under the prescribed conditions, the relative retentions with reference to paracetamol (retention time about 3 minutes) are: caffeine impurity B, about 0.6; 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) (10 ppm).

For all other impurities at 212 nm

Identify any peaks due to caffeine impurity B and E, and multiply the peak areas by a correction factor of 2.9 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) (100 ppm);

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, excluding paracetamol impurities J and K, 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 and 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 with a detection wavelength of 220 nm.

DETERMINATION OF CONTENT

Calculate the content of $C_{18}H_{21}NO_3,H_3PO_4,½H_2O$ in each tablet using the declared content of $C_{18}H_{21}NO_3,H_3PO_4,½H_2O$ 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, 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 $C_8H_9NO_2$ in the tablets 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 2% w/w or more 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, 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 with a detection wavelength of 220 nm.

DETERMINATION OF CONTENT

Calculate the content of $C_{18}H_{21}NO_3,H_3PO_4,½H_2O$ in the tablets using the declared content of $C_{18}H_{21}NO_3,H_3PO_4,½H_2O$ 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, 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 with a detection wavelength of 220 nm.

DETERMINATION OF CONTENT

Calculate the content of $C_8H_{10}N_4O_2$ in the tablets using the declared content of $C_8H_{10}N_4O_2$ 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, H, I and J listed under Codeine Phosphate, and impurities A, B, E and F listed under Caffeine.