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

Co-codamol Tablets

General Notices

Codeine Phosphate and Paracetamol Tablets

Action and use

Opioid analgesic + analgesic; antipyretic.

DEFINITION

Co-codamol Tablets contain Codeine Phosphate and Paracetamol.

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

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 paracetamol, $C_8H_9NO_2$

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* 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 of *codeine phosphate BPCRS* and *dihydrocodeine tartrate BPCRS* in *methanol (50%)*.

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 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.

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 which are different in colour.

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 (2) shows a peak with the same retention time as the principal peak in the chromatogram obtained with solution (1).

TESTS

Dissolution

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

TEST CONDITIONS

(a) Use Apparatus 2, rotating 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 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 in the mobile phase.

(1) After 45 minutes withdraw a sample of the medium and filter through a glass-fibre filter (Whatman GF/C is suitable). Dilute the filtrate with the medium, if necessary, to produce a solution expected to contain 0.0056% w/v of Paracetamol.
(2) 0.0056% w/v of *paracetamol BPCRS*.

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 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*.

DETERMINATION OF CONTENT

Calculate the total content of $C_8H_9NO_2$ 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) Shake with the aid of ultrasound a quantity of the powdered tablets containing 0.5 g of Paracetamol with 50 mL of solution A and filter (a regenerated cellulose membrane 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) 0.0005% 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 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: paracetamol impurity K, about 2.5; codeine impurity B, about 3.2; codeine, about 5.7; paracetamol impurity J, about 6.1; codeine impurity A, about 8.3 and codeine impurity C, about 8.7.

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

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 peak due to codeine in the chromatogram obtained with solution (2) (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 (excluding the peaks due to paracetamol impurities J and K):

any peak with a relative retention of 2.7 or less (with reference to paracetamol) and with an area less than half the area of the peak due to paracetamol in the chromatogram obtained with solution (7) (0.05%).

any peak with a relative retention greater than 2.7 (with reference to paracetamol) and with an area less than the area of the peak due to codeine in the chromatogram obtained with solution (7) (0.1%).

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 using the following method of analysis. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in the mobile phase.

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

(2) 0.004% w/v of *codeine phosphate BPCRS*.

CHROMATOGRAPHIC CONDITIONS

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

When the chromatograms are recorded under the prescribed conditions the retention time of codeine is about 8 minutes.

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 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 than of codeine phosphate

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

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

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 codeine phosphate, $C_{18}H_{21}NO_3,H_3PO_4,½H_2O$, in the tablets using the declared content of $C_{18}H_{21}NO_3,H_3PO_4,½H_2O$ in *codeine phosphate BPCRS*.

For paracetamol

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

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

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Dissolution may be used.

DETERMINATION OF CONTENT

Calculate the content of paracetamol, $C_8H_9NO_2$, in the tablets using the declared content of $C_8H_9NO_2$ in *paracetamol BPCRS*.

LABELLING

The label states the quantities of Codeine Phosphate and of Paracetamol in each tablet.

When Co-codamol Tablets are prescribed or demanded no strength being stated, tablets containing 8 mg of Codeine Phosphate and 500 mg of Paracetamol shall be dispensed or supplied.

IMPURITIES

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