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

Co-dydramol Tablets

General Notices

Dihydrocodeine and Paracetamol Tablets

Action and use

Opioid analgesic + analgesic; antipyretic.

DEFINITION

Co-dydramol Tablets contain Dihydrocodeine Tartrate and Paracetamol.

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

Content of dihydrocodeine tartrate, $C_{18}H_{23}NO_3,C_4H_6O_6$

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 30 mg of Dihydrocodeine Tartrate with 10 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 (Whatman GF/C is suitable).
(2) 0.1% w/v of *dihydrocodeine tartrate BPCRS* in *methanol (50%)*.
(3) 0.1% w/v each of *dihydrocodeine tartrate BPCRS* and *codeine phosphate 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 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 dihydrocodeine tartrate, 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 *0.2M potassium dihydrogen phosphate* 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 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* in the mobile phase.

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 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 a mixture of 22 volumes of *methanol* and 78 volumes of solution A.

Solution A: 0.223% w/v of *sodium pentanesulfonate* in *water*, adjusted to pH 2.8 with *2M hydrochloric acid*.

(1) Mix with the aid of ultrasound a quantity of the powdered tablets containing 0.5 g of Paracetamol in 40 mL. Dilute to 50 mL with the same diluent and filter (a regenerated cellulose membrane is suitable).
(2) Dilute 1 volume of solution (1) to 100 volumes.
(3) 0.0005% w/v each of *dihydrodeine tartrate BPCRS* and *codeine phosphate BPCRS* (dihydrocodeine tartrate impurity A).
(4) 0.0001% w/v of *4-aminophenol* (paracetamol impurity K)
(5) 0.00001% w/v of *4'-chloroacetanilide* (paracetamol impurity J)
(6) Dilute 1 volume of solution (2) to 10 volumes.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (3 µm) (Waters Atlantis T3 C18 is suitable).
(b) Use gradient elution and the mobile phase described below.
(c) Use a flow rate of 1.5 mL per minute.
(d) Use a column temperature of 45°.
(e) Use an autosampler temperature of 4°.
(e) Use detection wavelengths of 220 nm and 246 nm.
(f) Inject 50 µL of each solution.

MOBILE PHASE

Mobile phase A 2 volumes of *acetonitrile R1* and 98 volumes of solution A.

Mobile phase B *acetonitrile R1*.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-6	100	0	isocratic
6-18	100→93.9	0→6.1	linear gradient
18-30	93.9	6.1	isocratic
30-42	93.9→85.7	6.1→14.3	linear gradient
42-50	85.7→66.3	14.3→33.7	linear gradient
50-52	66.3→0	33.7→100	linear gradient
52-54.5	0	100	isocratic
54.5-55	0→100	100→0	linear gradient
55-65	100	0	re-equilibration

When the chromatograms are recorded under the prescribed conditions, the relative retentions with reference to paracetamol (retention time about 9 minutes) are: paracetamol impurity K, about 0.7; dihydrocodeine impurity B, about 2.3; dihydrocodeine, about 4.0; dihydrocodeine impurity A, about 4.1; dihydrocodeine impurity C, about 4.7; paracetamol impurity J, about 5.2; dihydrocodeine impurity D, about 5.3.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to dihydrocodeine and dihydrocodeine impurity A is at least 1.5 at 220 nm.

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 220 nm

Identify any peak corresponding to dihydrocodeine impurity A and multiply the area of this peak by a correction factor of 0.7.

In the chromatogram obtained with solution (1):

the area of any peak corresponding to dihydrocodeine impurity A is not greater than half the area of the principal peak in the chromatogram obtained with solution (2) (0.5%);

the area of any peak corresponding to dihydrocodeine impurities B, C, or D is not greater than 3 times the area of the principal peak in the chromatogram obtained with solution (6) (0.3% of each);

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* is not greater than the area of the peak due to paracetamol in the chromatogram obtained with solution (6) (0.1%).

The total impurity content, excluding dihydrocodeine impurities A to D, 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 (6) (0.05%)

Uniformity of content

Tablets containing less than 2 mg and/or less than 2% w/w of Dihydrocodeine Tartrate 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.

(1) Add 50 mL of *methanol* to one tablet and mix with the aid of ultrasound until completely dispersed. Add 100 mL of *water*, shake and dilute with sufficient *water* to produce a solution expected to contain 0.005% w/v of Dihydrocodeine Tartrate, filter through glass-fibre paper (Whatman GF/C is suitable) and use the filtrate.
(2) 0.005% w/v of *dihydrocodeine tartrate BPCRS* in *methanol (25%)*.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Dissolution may be used, but with a detection wavelength of 225 nm.

DETERMINATION OF CONTENT

Calculate the content of $C_{18}H_{23}NO_3,C_4H_6O_6$ in each tablet using the declared content of $C_{18}H_{23}NO_3,C_4H_6O_6$ in *dihydrocodeine tartrate BPCRS*.

ASSAY

For tablets containing the equivalent of less than 2 mg and/or less than 2% w/w of dihydrocodeine tartrate

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 dihydrocodeine tartrate

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 10 mg of Dihydrocodeine Tartrate with 50 mL of *methanol* for 1 minute, dilute with sufficient *water* to produce a solution containing 0.005% w/v of Dihydrocodeine Tartrate, shake for a further 10 minutes and filter through glass-fibre paper (Whatman GF/C is suitable) and use the filtrate.
(2) 0.005% w/v of *dihydrocodeine tartrate BPCRS* in *water.*

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Dissolution may be used, but with a detection wavelength of 225 nm.

DETERMINATION OF CONTENT

Calculate the content of dihydrocodeine tartrate, $C_{18}H_{23}NO_3,C_4H_6O_6$, in the tablets using the declared content of $C_{18}H_{23}NO_3,C_4H_6O_6$ in *dihydrocodeine tartrate BPCRS*.

For paracetamol

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 50 mL of *methanol* for 1 minute, dilute with sufficient *water* to produce a solution containing 0.005% w/v of Paracetamol, shake a further 10 minutes and filter through a glass-fibre paper (Whatman GF/C is suitable) and use the filtrate.
(2) 0.005% w/v of *paracetamol BPCRS* in *water*.

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 Dihydrocodeine Tartrate and of Paracetamol in each tablet.

Co-dydramol Tablets should be prescribed and dispensed by strength to minimise dispensing errors and the risk of accidental opioid overdose.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Dihydrocodeine Tartrate and impurities J and K under Paracetamol.