EAG/Panel/Working Party	EAG MC3
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Deadline for Comment	30 June 2017
Target Publication Date (subject to change)	BP2019
Notes: Revised Monograph: Related substances and Assay have been amended	

Dihydrocodeine Oral Solution

Dihydrocodeine Preparations

Action and use
Opioid receptor agonist; analgesic.

DEFINITION

Dihydrocodeine Oral Solution is a solution of Dihydrocodeine Tartrate in a suitable flavoured vehicle.

The oral solution complies with the requirements stated under Oral Liquids 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.

IDENTIFICATION

To a volume of the oral solution containing 20 mg of Dihydrocodeine Tartrate add 10 mL of *water* and extract with two 25 mL quantities of *cyclohexane*. Discard the cyclohexane extracts, add 3 mL of 5M *sodium hydroxide* to the aqueous layer, mix and extract with 25 mL of *cyclohexane*. Wash the cyclohexane layer with 10 mL of *water*, shake with *anhydrous sodium sulfate* and filter. Wash the filter with *cyclohexane* and evaporate the combined filtrate and washings to dryness. Dissolve the residue in 1 mL of *dichloromethane* and apply 0.2 mL drop wise on to the surface of a disc prepared using 0.3 g of *potassium bromide*, allowing the solvent to evaporate between applications, and dry the disc at 50° for 2 minutes. The *infrared absorption spectrum*, Appendix II A, is concordant with the *reference spectrum* of dihydrocodeine *(RS 102)*.

TESTS

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

(1) Dilute a quantity of the oral solution to produce a solution containing 0.1% w/v of Dihydrocodeine Tartrate.

(2) Dilute 1 volume of solution (1) to 200 volumes.

(3) 0.04% w/v each of *dihydrocodeine tartrate BPCRS* and *codeine phosphate BPCRS*.

(4) Dilute 1 volume of solution (2) to 5 volumes.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octylsilyl silica gel for chromatography* (5µm) (Hypersil Gold C8 is suitable).

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

(c) Use a flow rate of 1 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 284 nm.

(f) Inject 20 µL of each solution.

(g) Allow the chromatography to proceed for 4 times the retention time of dihydrocodeine.

MOBILE PHASE

Mobile phase A To 1.0 g of *sodium heptanesulfonate*, add 10.0 mL of *glacial acetic acid* and 4.0 mL of a solution of 5.0 mL of *triethylamine* diluted to 25.0 mL with a mixture of equal volumes of *acetonitrile* and *water*. Add 170 mL of *acetonitrile* and dilute to 1000 mL with *water*.

Mobile phase B acetonitrile

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0 – 20	100	0	isocratic
20 – 25	100→20	0→80	linear gradient
25 – 40	20	80	isocratic
40 – 45	20→100	80→0	linear gradient
45 – 50	100	0	re-equilibration

When the chromatograms are recorded under the prescribed conditions the retention time of dihydrocodeine is about 11 minutes. The retention time relative to dihydrocodeine of impurity A is about 1.1.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to dihydrocodeine and codeine is at least 2.0.

LIMITS

In the chromatogram obtained with solution (1):

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

the area of any other *secondary peaks* is not greater than 0.6 times the area of the principal peak in the chromatogram obtained with solution (2) (0.3%).

the sum of the areas of any *secondary peaks* is not greater than twice the area of the principal peak in the chromatogram obtained with solution (2) (1.0%).

Disregard any peak due to tartaric acid or with an area less than the area of the principal peak in the chromatogram obtained with solution (4) (0.1%).

ASSAY

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

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(1) Disperse a weighed quantity of the oral solution containing 25 mg of Dihydrocodeine Tartrate in 25 mL of *mobile phase A* and filter. Dilute 1 volume to 10 volumes with *mobile phase A*.

(2) 0.01% w/v of *dihydrocodeine tartrate BPCRS* in *water*.

(3) 0.04% w/v each of *dihydrocodeine tartrate BPCRS* and *codeine phosphate BPCRS*.

CHROMATOGRAPHIC CONDITIONS

Use the conditions described under Related substances.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to dihydrocodeine and codeine is at least 2.0.

DETERMINATION OF CONTENT

Determine the *weight per mL* of the oral solution, Appendix V G, and calculate the content of $C_{18}H_{23}NO_3$, $C_4H_6O_6$, weight in volume, using the declared content of $C_{18}H_{23}NO_3$, $C_4H_6O_6$ in *dihydrocodeine tartrate BPCRS*.

STORAGE

Dihydrocodeine Oral Solution should be protected from light.

IMPURITIES

The impurities limited by the requirements of this monograph those listed under Dihydrocodeine Tartrate.