EAG/Panel/Working Party	EAG MC3
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Deadline for Comment	30 June 2017
Target Publication Date (subject to change)	BP2019
Notes:New Monograph	

Prolonged-release Dihydrocodeine Tablets

Dihydrocodeine Preparations

Action and use
Opioid receptor agonist; analgesic.

DEFINITION
Prolonged release Dihydrocodeine Tablets contain Dihydrocodeine Tartrate.They are formulated so that the medicament is released over a period of several hours.

PRODUCTION
A suitable dissolution test is carried out to demonstrate the appropriate release of Dihydrocodeine Tartrate. The dissolution profile reflects the *in vivo* performance which in turn is compatible with the dosage schedule recommended by the manufacturer.

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.

IDENTIFICATION
Mix a quantity of the powdered tablets containing 100 mg of Dihydrocodeine Tartrate and 4 mL of *water* with the aid of ultrasound and filter. Add 4 mL of *dichloromethane* and 0.5 mL of *strong sodium hydroxide solution* to the filtrate, mix and centrifuge. Isolate the lower layer and evaporate to dryness. The *infrared absorption spectrum* of the dried residue, Appendix II A, is concordant with the *reference spectrum* of dihydrocodeine tartrate (*RS XXX*).

TESTS

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

(1) Mix a quantity of the powdered tablets containing 50 mg of Dihydrocodeine Tartrate and 25 mL of the mobile phase with the aid of ultrasound, dilute to 50 mL and filter.

(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 isocratic 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

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*.

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

(1) Mix a quantity of the powdered tablets containing 50 mg of Dihydrocodeine Tartrate and 25 mL of *mobile phase* with the aid of ultrasound, dilute to 50 mL with *mobile phase*. Dilute 1 volume to 10 volumes with *mobile phase*.

(2) 0. 01% w/v of *dihydrocodeine tartrate BPCRS* in *mobile phase*.

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(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

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

STORAGE

Prolonged- release Dihydrocodeine Tablets should be protected from light.

IMPURITIES

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