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

Capecitabine Tablets

General Notices

Action and use

Pyrimidine analogue; cytotoxic; treatment of cancer.

DEFINITION

Capecitabine Tablets contain Capecitabine.

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

Content of capecitabine, $C_{15}H_{22}FN_3O_6$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

Shake a quantity of the powdered tablets containing 0.05 g of Capecitabine with 4 mL of *ethanol* and filter. Evaporate the filtrate to dryness, under a stream of nitrogen, on a water bath at 65°. The *infrared absorption spectrum* of the residue, Appendix II A, is concordant with the reference spectrum of *capecitabine BPCRS* treated in the same manner.

TESTS

Dissolution

Carry out the following procedure protected from light. 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 900 mL of *phosphate buffer pH 6.8*, at a temperature of 37°, as the medium.

PROCEDURE

(1) After 30 minutes withdraw a sample of the dissolution medium and filter. Use the filtered medium, diluted with *phosphate buffer pH 6.8*, if necessary, to produce a solution expected to contain 0.017% w/v of Capecitabine.
(2) 0.017% w/v of *capecitabine BPCRS* in *phosphate buffer pH 6.8*.
(3) 0.017% w/v of *capecitabine BPCRS* and 0.000025% w/v of *capecitabine impurity D EPCRS* in *phosphate buffer pH 6.8*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (5 µm) (Zorbax Eclipse XDB-C18 is suitable).
(b) Use gradient elution and the mobile phase described below.
(c) Use a flow rate of 1 mL per minute.
(d) Use a column temperature of 40°.
(e) Use a detection wavelength of 250 nm.
(f) Inject 40 µL of each solution.

MOBILE PHASE

Mobile phase A 5 volumes of *acetonitrile*, 35 volumes of *methanol* and 60 volumes of a 0.1% v/v solution of *glacial acetic acid*.

Mobile phase B 5 volumes of *acetonitrile*, 80 volumes of *methanol* and 15 volumes of a 0.1% v/v solution of *glacial acetic acid*.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-5	100	0	isocratic
5-20	100→49	0→51	linear gradient
20-30	49	51	isocratic
30-32	49→100	51→0	linear gradient
32-40	100	0	re-equilibration

SYSTEM SUITABILITY

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

DETERMINATION OF CONTENT

Calculate the content of $C_{15}H_{22}FN_3O_6$ in the medium using the declared content of $C_{15}H_{22}FN_3O_6$ in *capecitabine BPCRS*.

LIMITS

The amount of capecitabine 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. *Prepare the solutions immediately before use.*

Solvent A 5 volumes of *acetonitrile*, 35 volumes of *methanol* and 60 volumes of *water*.

(1) Shake a quantity of powdered tablets containing 60 mg of Capecitabine with 80 mL of solvent A, dilute to 100 mL with the solvent A and filter.
(2) Dilute 1 volume of solution (1) to 100 volumes with solvent A.
(3) Dilut1 2 volume of solution (2) to 5 volumes with solvent A.
(4) 0.06% w/v of *capecitabine BPCRS* and 0.0001% w/v each of *capecitabine impurity A EPCRS*, *capecitabine impurity B EPCRS* and *capecitabine impurity D EPCRS* in solvent A.

The chromatographic conditions described under Dissolution may be used with an injection volume of 10 µL.

When chromatograms are recorded under the prescribed conditions, the retention times relative to capecitabine (retention time, about 16 minutes) are: impurity A, about 0.16; impurity B, about 0.18; impurities D and E (co-elute), 0.94.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (4):

the *resolution* between the peaks due to impurity A and impurity B is at least 1.5;

the *resolution* between the peaks due to impurity D and capecitabine is at least 2.0.

LIMITS

Identify any peak corresponding to impurity B using the chromatogram obtained with solution (4) and multiply the peak area by the *correction factor* of 1.3.

In the chromatogram obtained with solution (1):

the area of any peak due to impurity A or impurity B is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (1%);

the sum of the areas of any peak due to impurities D and E is not greater than half the area of the principal peak in the chromatogram obtained with solution (2) (0.5%);

the area of any other *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (3) (0.2%);

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

Disregard any peak with an area less than 0.25 times the area of the principal peak in the chromatogram obtained with solution (3) (0.05%).

ASSAY

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

Solvent A 5 volumes of *acetonitrile*, 35 volumes of *methanol* and 60 volumes of *water*.

(1) Shake a quantity of powdered tablets containing 60 mg of Capecitabine with 80 mL of solvent A, dilute to 100 mL with the solvent A and filter.
(2) 0.06% w/v of *capecitabine BPCRS* in solvent A.
(3) 0.06% w/v of *capecitabine BPCRS* and 0.0001% w/v of *capecitabine impurity D EPCRS* in solvent A.

The chromatographic conditions described under Dissolution may be used with an injection volume of 10 µL.

SYSTEM SUITABILITY

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

DETERMINATION OF CONTENT

Calculate the content of $C_{15}H_{22}FN_3O_6$ in the tablets using the declared content of $C_{15}H_{22}FN_3O_6$ in *capecitabine BPCRS*.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under *Capecitabine*.