IDENTIFICATION

- **A. INFRARED ABSORPTION ⟨197K⟩:** If the spectra obtained show differences, proceed with the samples prepared as follows. Separately dissolve a quantity of USP Candesartan Cilexetil RS and Candesartan Cilexetil in alcohol. [NOTE—Heating the solution may be necessary for complete dissolution.] Cool the solution in an ice bath, filter the crystals, and dry at 105°.
- **B.** The retention time of the major peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the procedure for *Organic Impurities*.

ASSAY

- **PROCEDURE**

Sample solution: 8.33 mg/mL of Candesartan Cilexetil in glacial acetic acid

Titrimetric system

(See *Titrimetry* ⟨541⟩.)

Mode: Potentiometric

Titrant: 0.1 N perchloric acid

Analysis: Titrate with 8 mL of 0.1 N perchloric acid VS using a blank determination under the same conditions. Each mL of the *Titrant* is equivalent to 61.07 mg of $C_{33}H_{34}N_6O_6$.

Acceptance criteria: 98.7%–101.0% on the anhydrous basis

IMPURITIES

Inorganic Impurities

- **RESIDUE ON IGNITION ⟨281⟩:** NMT 0.1%, determined from a 1-g sample

Organic Impurities

- **PROCEDURE**

Diluent: Acetonitrile and water (3:2)

Solution A: Acetonitrile, glacial acetic acid, and water (57:1:43)

Solution B: Acetonitrile, glacial acetic acid, and water (90:1:10)

Mobile phase: See the gradient table below.

Time (min)	Solution A (%)	Solution B (%)
0	100	0
30	0	100

[NOTE—Equilibration for about 10 min may be necessary between injections.]

System suitability solution: 0.04 mg/mL of USP Candesartan Cilexetil RS and 0.125 mg/mL of acenaphthene in *Diluent*

Standard solution: 4 µg/mL of USP Candesartan Cilexetil RS in *Diluent*

Sample solution: 0.4 mg/mL of Candesartan Cilexetil in *Diluent*

Chromatographic system

(See *Chromatography* ⟨621⟩, *System Suitability*.)

Mode: LC

Detector: UV 254 nm

Column: 3.9-mm × 15-cm; 4-µm packing L1

Flow rate: 0.8 mL/min

Injection size: 10 µL

System suitability

[NOTE—The *Mobile phase* used for testing system suitability is 100% *Solution A* in an isocratic mode.]

Sample: *System suitability solution*

Suitability requirements

Resolution: NLT 5.0 between candesartan cilexetil and acenaphtene

Tailing factor: NMT 1.5 for candesartan cilexetil

Relative standard deviation: NMT 3.0% for the candesartan cilexetil peak

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of each individual impurity in the portion of Candesartan Cilexetil taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times 100$$

r_U = peak response of each individual impurity from the *Sample solution*

r_S = peak response of candesartan cilexetil from the *Standard solution*

C_S = concentration of USP Candesartan Cilexetil RS in the *Standard solution* (mg/mL)

C_U = concentration of Candesartan Cilexetil in the *Sample solution* (mg/mL)

Acceptance criteria

Individual impurities: See *Table 1*.

Total impurities: NMT 0.6%. [NOTE— Calculate the total impurities from the sum of all impurity peaks greater than or equal to 0.05%.]

Table 1

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Ethyl candesartan[a]	0.4	0.2
Desethyl candesartan cilexetil[b]	0.5	0.3
Candesartan cilexetil	1.0	—
*N*2-Ethyl candesartan cilexetil[c]	2.0	0.2
Any other unknown impurity	—	0.10

[a] Ethyl 1-{[2′-(1*H*-tetrazol-5-yl)biphenyl-4-yl]methyl}-2-ethoxybenzimidazole-7-carboxylate.

[b] ±1-(Cyclohexyloxycarbonyloxy)ethyl 1-{[2′-(1*H*-tetrazol-5-yl)biphenyl-4-yl]methyl}-2-oxobenzimidazole-7-carboxylate.

[c] ±1-(Cyclohexyloxycarbonyloxy)ethyl 2-ethoxy-1-{[2′-(*N*-ethyl-tetrazol-5-yl) biphenyl-4-yl]methyl}benzimidazole-7-carboxylate.

SPECIFIC TESTS

- **WATER DETERMINATION,** *Method 1* ⟨**921**⟩**:** NMT 0.3%

ADDITIONAL REQUIREMENTS

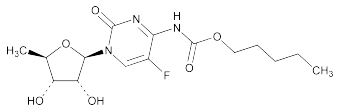
- **PACKAGING AND STORAGE:** Preserve in tight containers, and store at controlled room temperature.
- **USP REFERENCE STANDARDS ⟨11⟩**

USP Candesartan Cilexetil RS

1*H*-Benzimidazole-7-carboxylic acid, 2-ethoxy-1-[[2′-(1*H*-tetrazol-5-yl)[1,1′-biphenyl]-4-yl]methyl]-, 1-[[(cyclohexyloxy)carbonyl]oxy]ethyl ester, (±); (±)-1-Hydroxyethyl 2-ethoxy-1-[*p*-(*o*-1*H*-tetrazol-5-ylphenyl)benzyl]-7-benzimidazolecarboxylate, cyclohexyl carbonate (ester).

610.66

Capecitabine



$C_{15}H_{22}FN_3O_6$ 359.35

Carbamic acid, [1-(5-deoxy-β-D-ribofuranosyl)-5-fluoro-1,2-dihydro-2-oxo-4-pyrimidinyl]-, pentyl ester;

Pentyl 1-(5-deoxy-β-D-ribofuranosyl)-5-fluoro-1,2-dihydro-2-oxo-4-pyrimidinecarbamate [154361-50-9].

DEFINITION

Capecitabine contains NLT 98.0% and NMT 102.0% of $C_{15}H_{22}FN_3O_6$, calculated on the anhydrous and solvent-free basis.

IDENTIFICATION

- **A. Infrared Absorption** ⟨197K⟩
  Sample: 2 mg of sample in 300 mg of potassium bromide
- **B.** The retention time of the major peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay.*

ASSAY

- **Procedure**
  Diluent: Methanol, acetonitrile, and water (7:1:12)
  Solution A: 0.1% mixture of glacial acetic acid in water
  Solution B: Methanol, acetonitrile, and *Solution A* (7:1:12)
  Solution C: Methanol, acetonitrile, and *Solution A* (16:1:3)
  Mobile phase: See the gradient table below.

Time (min)	Solution B (%)	Solution C (%)
0	100	0
5	100	0
20	49	51
30	49	51
31	100	0
40	100	0

[NOTE—The following solutions may be sonicated if necessary.]
System suitability solution: 0.6 µg/mL each of USP Capecitabine RS, USP Capecitabine Related Compound A RS, USP Capecitabine Related Compound B RS, and USP Capecitabine Related Compound C RS in *Diluent*
Standard solution: 0.6 mg/mL of USP Capecitabine RS in *Diluent*
Sample solution: 0.6 mg/mL of Capecitabine in *Diluent*
Chromatographic system
(See *Chromatography* ⟨621⟩, *System Suitability*.)
Mode: LC
Detector: UV 250 nm
Column: 4.6-mm × 25-cm; 5-µm packing L1
Column temperature: 40°
Autosampler temperature: 5°
Flow rate: 1 mL/min
Injection size: 10 µL
System suitability
Samples: *System suitability solution* and *Standard solution*
[NOTE—For the purpose of peak identification, the approximate relative retention times are given in *Impurity Table 1*. The relative retention times are measured with respect to capecitabine.]
Suitability requirements
Resolution: NLT 1.0 between capecitabine related compound A and capecitabine related compound B, *System suitability solution*
Tailing factor: NMT 1.5, *Standard solution*
Relative standard deviation: NMT 2.0%, *Standard solution*
Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the percentage of $C_{15}H_{22}FN_3O_6$ in the portion of Capecitabine taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times 100$$

r_U = peak response from the *Sample solution*
r_S = peak response from the *Standard solution*
C_S = concentration of USP Capecitabine RS in the *Standard solution* (mg/mL)
C_U = concentration of Capecitabine in the *Sample solution* (mg/mL)
Acceptance criteria: 98.0%–102.0% on the anhydrous and solvent-free basis

IMPURITIES

Inorganic Impurities

- **Residue on Ignition** ⟨281⟩**:** NMT 0.1%
- **Heavy Metals,** *Method II* ⟨231⟩**:** NMT 20 ppm

Organic Impurities

- **Procedure**
  Diluent, Solution B, Solution C, System suitability solution, Standard solution, Sample solution, and **Chromatographic system:** Proceed as directed in the *Assay*.
  Analysis
  Samples: *Standard solution* and *Sample solution*
  Calculate the percentage of each impurity in the portion of Capecitabine taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times 100/F$$

r_U = peak response for each impurity from the *Sample solution*
r_S = peak response for capecitabine from the *Standard solution*
C_S = concentration of USP Capecitabine RS in the *Standard solution* (mg/mL)
C_U = concentration of Capecitabine in the *Sample solution* (mg/mL)
F = relative response factor for an impurity, from *Impurity Table 1*
Acceptance criteria
Individual impurities: See *Impurity Table 1*.
Total impurities: NMT 1.5%

Impurity Table 1

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Capecitabine related compound A	0.18	1.05	0.3
Capecitabine related compound B	0.19	0.81	0.3
2′,3′-Di-*O*-acetyl-5′-deoxy-5-fluorocytidine	0.36	0.89	0.1
5′-Deoxy-5-fluoro-N4-(2-methyl-1-butyloxy-carbonyl)cytidine + 5′-Deoxy-5-fluoro-N4-(3-methyl-1-butyloxycarbonyl)cytidine	0.95	1.01	0.5
Capecitabine	1.00	1.00	—
[1-[5-Deoxy-3-*O*-(5-deoxy-β-D-ribofuranosyl)-β-D-ribofuranosyl]-5-fluoro-2-oxo-1,2-dihydropyrimidin-4-yl]-carbamic acid pentyl ester	1.06	1.00	0.3

Impurity Table 1 *(Continued)*

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
[1-[5-Deoxy-2-*O*-(5-deoxy-β-D-ribofuranosyl)-β-D-ribofuranosyl]-5-fluoro-2-oxo-1,2-dihydropyrimidin-4-yl]-carbamic acid pentyl ester	1.09	1.00	0.2
Capecitabine related compound C	1.11	0.91	0.3
[1-[5-Deoxy-3-*O*-(5-deoxy-α-D-ribofuranosyl)-β-D-ribofuranosyl]-5-fluoro-2-oxo-1,2-dihydropyrimidin-4-yl]-carbamic acid pentyl ester	1.20	1.00	0.3
2′,3′-Di-*O*-acetyl-5′-deoxy-5-fluoro-N4-(pentyloxycarbonyl)cytidine	1.37	0.85	0.1
Individual unspecified impurity	—	1.00	0.1

SPECIFIC TESTS

- **OPTICAL ROTATION,** *Specific Rotation* ⟨**781S**⟩**:** +96.0° to +100.0°
  Sample solution: 10 mg/mL, on the anhydrous and solvent-free basis, in methanol, at 20°
- **WATER DETERMINATION,** *Method Ic* ⟨**921**⟩**:** NMT 0.3%

ADDITIONAL REQUIREMENTS

- **PACKAGING AND STORAGE:** Preserve in tight containers. Store at controlled room temperature.
- **USP REFERENCE STANDARDS** ⟨**11**⟩
  USP Capecitabine RS
  USP Capecitabine Related Compound A RS
  5′-Deoxy-5-fluorocytidine.
  $C_9H_{12}FN_3O_4$ 245.21
  USP Capecitabine Related Compound B RS
  5′-Deoxy-5-fluorouridine.
  $C_9H_{11}FN_2O_5$ 246.19
  USP Capecitabine Related Compound C RS
  2′,3′-*O*-Carbonyl-5′-deoxy-5-fluoro-*N*⁴-(pentyloxycarbonyl)cytidine.
  $C_{16}H_{20}FN_3O_7$ 385.34

Capecitabine Tablets

DEFINITION

Capecitabine Tablets contain NLT 93.0% and NMT 105.0% of the labeled amount of capecitabine ($C_{15}H_{22}FN_3O_6$).

IDENTIFICATION

- **A. INFRARED ABSORPTION** ⟨**197K**⟩
  Analytical wave number: 1500–1760 cm^{-1}
  Sample: Grind 1 Tablet to a fine powder with a mortar and pestle. Mix 1 mg of this sample with 300 mg of potassium bromide.
- **B.** The retention time of the major peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay.*

ASSAY

- **PROCEDURE**
  Diluent: Methanol, acetonitrile, and water (7:1:12)
  Solution A: 0.1% mixture of glacial acetic acid in water
  Solution B: Methanol, acetonitrile, and *Solution A* (7:1:12)
  Solution C: Methanol, acetonitrile, and *Solution A* (16:1:3)
  Mobile phase: See the gradient table below.

Time (min)	Solution B (%)	Solution C (%)
0	100	0
5	100	0
20	49	51
30	49	51
31	100	0
40	100	0

[NOTE—The following solutions may be sonicated as necessary.]
System suitability solution: Includes 0.6 µg/mL of USP Capecitabine RS, 0.6 µg/mL of USP Capecitabine Related Compound A RS, 0.6 µg/mL of USP Capecitabine Related Compound B RS, and 0.6 µg/mL of USP Capecitabine Related Compound C RS in *Diluent*
Standard solution: 0.6 mg/mL of USP Capecitabine RS in *Diluent*
Sample solution: Equivalent to 0.6 mg/mL of capecitabine, from powdered Tablets (NLT 20), in *Diluent.* [NOTE—Pass through a PVDF membrane filter of 0.45-µm pore size, and use the filtrate.]
Chromatographic system
(See *Chromatography* ⟨621⟩*, System Suitability.*)
Mode: LC
Detector: UV 250 nm
Column: 4.6-mm × 25-cm; 5-µm packing L1
Column temperature: 40°
Autosampler temperature: 5°
Flow rate: 1 mL/min
Injection size: 10 µL
System suitability
Samples: *System suitability solution* and *Standard solution*
[NOTE—For the purpose of peak identification, the approximate relative retention times are given in *Impurity Table 1*. The relative retention times are measured with respect to capecitabine.]
Suitability requirements
Resolution: NLT 1.0 between capecitabine related compound A and capecitabine related compound B, *System suitability solution*
Tailing factor: NMT 1.5, *Standard solution*
Relative standard deviation: NMT 2.0%, *Standard solution*
Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the percentage of $C_{15}H_{22}FN_3O_6$ in the portion of Tablets taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times 100$$

r_U = peak response from the *Sample solution*
r_S = peak response from the *Standard solution*
C_S = concentration of USP Capecitabine RS in the *Standard solution* (mg/mL)
C_U = nominal concentration of capecitabine in the *Sample solution* (mg/mL)