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Clarithromycin Tablets

General Notices

Details for the public consultation of this monograph are as follows:

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Notes:	**REVISED** Dissolution and Assay system suitability updated. If limits are too restrictive, please provide batch/stability data to demonstrate that an increase is required.

Action and use

Macrolide antibacterial.

DEFINITION

Clarithromycin Tablets contain *Clarithromycin*.

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

Content of clarithromycin, $C_{38}H_{69}NO_{13}$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

Shake a quantity of the powdered tablets containing 0.5 g of Clarithromycin with 10 mL of *water* and extract with 20 mL of *dichloromethane*. Separate the lower dichloromethane layer and centrifuge. Filter the supernatant (Whatman GF/C is suitable) and evaporate to dryness. The *infrared absorption spectrum* of the residue, Appendix II A, after drying under vacuum at room temperature for 2 hours, is concordant with the *reference spectrum A* of clarithromycin *(RS 424)*.

TESTS

Dissolution

Carry out the *dissolution test for tablets and capsules*, Appendix XII BI.

TEST CONDITIONS

(a) Use Apparatus 2, rotating the paddle at 50 revolutions per minute.
(b) Use 900 mL of a solution containing 1000 volumes of a 1.361% w/v solution of *sodium acetate* and 350 volumes of 0.1M *acetic acid*, adjusted to pH 5.0 with 0.1M *acetic acid*, at a temperature of 37º± 0.5º, as the medium.

PROCEDURE

After 45 minutes, withdraw a sample of the medium and filter. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Use the filtered dissolution medium, diluted with mobile phase if necessary, to produce a solution expected to contain 0.011% w/v of Clarithromycin.
(2) 0.011% w/v of *clarithromycin BPCRS* in the mobile phase.
(3) 0.15% w/v of *clarithromycin for peak identification EPCRS* in the mobile phase.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (5 µm) (Superspher ODS2 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 a column temperature of 50°.
(e) Use a detection wavelength of 210 nm.
(f) Inject 25 µL of each solution.

MOBILE PHASE

35 volumes of 0.067M *potassium dihydrogen orthophosphate* and 65 volumes of *methanol* adjusted to pH 4.0 with *orthophosphoric acid*.

When the chromatograms are recorded under the prescribed conditions the approximate retention times for clarithromycin and clarithromycin impurity E are 4 and 6 minutes respectively.

DETERMINATION OF CONTENT

Calculate the total content of clarithromycin, $C_{38}H_{69}NO_{13}$, in the medium using the declared content of $C_{38}H_{69}NO_{13}$ in *clarithromycin BPCRS*.

Related substances

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

(1) Disperse a quantity of powdered tablets containing 75 mg of Clarithromycin in 40 mL of a mixture of equal volumes of *acetonitrile R1* and *water* (solution A), mix with the aid of ultrasound, add sufficient solution A to produce 50 mL and filter through a Whatman GF/C filter and then through a 0.45-µm PTFE filter.
(2) Dilute 5 volumes of solution (1) to 100 volumes with solution A.
(3) Dilute 10 volumes of solution (2) to 100 volumes with solution A.
(4) 0.15% w/v of *clarithromycin for peak identification EPCRS* in solution A.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (10 cm x 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (3 µm) (Hypersil BDS is suitable).
(b) Use gradient elution and the mobile phases described below.
(c) Use a flow rate of 1.1 mL per minute.
(d) Use a column temperature of 40°.
(e) Use a detection wavelength of 205 nm.
(f) Inject 10 µL of each solution.

MOBILE PHASE

Mobile phase A A 0.476% w/v solution of *potassium dihydrogen orthophosphate*, adjusted to pH 4.4 with either 2M *orthophosphoric acid* or a 4.5% w/v solution of *potassium hydroxide*, filtered through a C18 filtration kit (3M Empore is suitable).

Mobile phase B *acetonitrile R1*.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-32	75→40	25→60	linear gradient
32-34	40	60	isocratic
34-36	40→75	60→25	linear gradient
36-42	75	25	re-equilibration

When the chromatograms are recorded using the prescribed conditions the retention times relative to clarithromycin (retention time = about 11 minutes) are: impurity I = about 0.38; impurity A = about 0.42; impurity J = about 0.63; impurity L = about 0.74; impurity B = about 0.79; impurity M = about 0.81; impurity C = about 0.89; impurity D = about 0.96; impurity N = about 1.15; impurity E = about 1.27; impurity F = about 1.33; impurity P = about 1.35; impurity O = about 1.41; impurity K = about 1.59; impurity G = about 1.72; impurity H = about 1.82.

SYSTEM SUITABILITY

The test is not valid unless:

in the chromatogram obtained with solution (2) the *symmetry factor* of the peak due to clarithromycin is less than 1.75;

in the chromatogram obtained with solution (4) the *peak-to-valley ratio* is at least 3.0 where H_p is the height above the baseline of the peak due to impurity D and H_v is the height above the baseline of the lowest point of the curve separating this peak from the peak due to clarithromycin;

the chromatogram obtained with solution (4) closely resembles the chromatogram supplied with *clarithromycin for peak identification EPCRS*.

LIMITS

Identify any peaks in the chromatogram obtained with solution (1) corresponding to impurities G and H using solution (4) and multiply the areas of these peaks by the corresponding correction factors; impurity G, 0.27; impurity H, 0.15.

In the chromatogram obtained with solution (1):

the area of any *secondary peak* is not greater than twice the area of the principal peak in the chromatogram obtained with solution (3) (1%) and not more than four such peaks have an area greater than 0.8 times the area of the principal peak in the chromatogram obtained with solution (3) (0.4%);

the sum of the areas of all the *secondary peaks* is not greater than 7 times the area of the principal peak in the chromatogram obtained with solution (3) (3.5%).

Disregard any peak with an area less than 0.2 times the area of the principal peak in the chromatogram obtained with solution (3) (0.1%). Disregard any peaks eluting before impurity I and after impurity H.

ASSAY

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

(1) Finely powder a quantity of tablets containing 2 g of Clarithromycin and quantitatively transfer the powder to a volumetric flask using about 350 mL of *methanol*. Mix with the aid of ultrasound for 15 minutes, shake vigorously for 15 minutes, allow to cool, add sufficient *methanol* to produce 500 mL and mix. Filter the solution (Whatman GF/C paper is suitable), dilute 1 volume of the filtrate to 40 volumes with mobile phase and filter through a 0.45-µm filter.
(2) 0.01% w/v of *clarithromycin BPCRS* in the mobile phase.
(3) 0.15% w/v of *clarithromycin for peak identification EPCRS* in the mobile phase.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Dissolution may be used.

When the chromatograms are recorded under the prescribed conditions the approximate retention times for clarithromycin and clarithromycin impurity E are 4 and 6 minutes respectively.

DETERMINATION OF CONTENT

Calculate the content of $C_{38}H_{69}NO_{13}$ in the tablets using the declared content of $C_{38}H_{69}NO_{13}$ in *clarithromycin BPCRS*.