Doxycycline tablets (Doxycyclini compressi)

2020-01

Category. Antibacterial and antimalarial.

Storage. Doxycycline tablets should be kept in a tightly closed container.

Labelling. The designation on the container of doxycycline tablets should state that the active ingredient is in the hyclate form and the quantity should be indicated in terms of the equivalent amount of doxycycline ($C_{22}H_{24}N_2O_8$).

Additional information. Strengths in the current WHO Model list of essential medicines (EML): 50 mg, 100 mg (as hyclate). Strengths in the current WHO Model list of essential medicines EML for children: 50 mg, 100 mg (as hyclate).

Requirements

Comply with the monograph for *Tablets*.

Definition. Doxycycline tablets contain Doxycycline hyclate. They contain not less than 90.0% and not more than 110.0% of the amount of doxycycline ($C_{22}H_{24}N_2O_8$) stated on the label.

Identity tests

-Either tests A and F or tests B and F or tests C, D and F may be applied.

Carry out the test as described under *1.14.1 Chromatography*, Thin-layer chromatography using silica gel R4 as the coating substance and a mixture of 12 volumes of ethyl acetate R, 12 volumes of acetic acid glacial R, 8 volumes of methanol R and 2 volumes of ammonia R as the mobile phase. Apply separately to the plate 2 µL of each of the following three solutions. For solution (A), shake a quantity of the contents of the powdered tablets containing the equivalent of about 8 mg of doxycycline in 10 mL of methanol R, filter and use the resulting solution. For solution (B), dissolve 10 mg of doxycycline hyclate RS in methanol R and dilute to 10 mL with the same solvent. For solution (C), dissolve 10 mg of tetracycline hydrochloride RS in 10 mL of solution (B). After removing the plate from the chromatographic chamber, allow it to dry in a current of air and examine the chromatogram in ultraviolet light (254nm).

The principal spot obtained with solution A corresponds in position, appearance and intensity with that obtained with solution B. The test is not valid unless the chromatogram obtained with solution (C) shows two clearly separated spots.

See the method described below under "Assay". The retention time of the principal peak in the chromatogram obtained with solution (1) corresponds to that in the chromatogram obtained with solution (2).

To a quantity of the powdered tablets containing the equivalent of about 2 mg of doxycycline, add about 5 mL of sulfuric acid (~1760 g/L) TS; an intense yellow colour is produced.

To a quantity of the powdered tablets containing the equivalent of about 0.1 g of doxycycline, add 10 mL of water R, filter and use the filtrate for the following tests.

To 2.0 mL of the filtrate, add 1 drop of ferric chloride (25 g/L) TS; a dark red-brown colour is produced.

To 1.0 mL of the filtrate, add 5 drops of silver nitrate (40 g/L) TS; a white, curdy precipitate is formed which dissolves in 1.0 mL of ammonia (~100 g/L) TS.

Dissolution. Carry out the test as described under *5.5 Dissolution test for solid oral dosage forms* using as the dissolution medium, 500 mL of dissolution buffer, pH 6.8, TS and rotating the paddle at 75 revolutions per minute. At 30 minutes, withdraw a sample of 10 mL of the medium through an in-line filter. Measure the absorbance (*1.6*) of a 1 cm layer of the filtered sample, suitably diluted if necessary, at the maximum at about 274 nm. At the same time, measure the absorbance at the maximum at about 274 nm of a suitable solution of doxycycline hyclate RS in dissolution buffer, pH 6.8, TS, using the same buffer as the blank.

For each of the tablets tested, calculate the total amount of doxycycline ($C_{22}H_{24}N_2O_8$) in the medium. Evaluate the results as described under *5.5 Dissolution test for solid oral dosage forms*, Acceptance criteria. The amount of doxycycline released is not less than 75% (Q) of the amount declared on the label.

Related substances. Carry out the test as described under *1.14.1 Chromatography*, High-performance liquid chromatography using the chromatographic conditions and preparing the solutions as described under "Assay".

Inject 20 µL of solution (5). The test is not valid unless the resolution between the first peak (metacycline) and the second peak (6-epidoxycycline) is greater than 1.25 and the resolution between the second peak and the third peak (doxycycline) is greater than 2.0. If necessary, adjust the *tert*-butanol R content in the mobile phase mobile phase to obtain a long retention time for doxycycline and to improve the separation of doxycycline and related substances. The test is not valid unless the symmetry factor

for the third peak is less than 1.25.

In the chromatogram obtained with solution (1), the area of any peak corresponding to metacycline or to 6-epidoxycycline is not greater than the area of the corresponding peak in the chromatogram obtained with solution (6) (2% with reference to doxycycline hyclate), the area of any peak appearing between the solvent peak and the peak corresponding to metacycline and the area of any peak appearing on the tail of the main peak is not greater than 0.25 times the area of the peak corresponding to 6-epidoxycycline in the chromatogram obtained with solution (6) (0.5% with reference to doxycycline hyclate).

Assay. Weigh and powder 20 tablets. Carry out the test as described under *1.14.1 Chromatography*, High-performance liquid chromatography using a stainless steel column (25 cm × 4.6 mm) packed with particles of styrene-divinylbenzene copolymer (8-10 µm). As the mobile phase, use a solution prepared as follows: transfer 60.0 g of *tert*-butanol R with the aid of 200 mL of water R to a 1000 mL volumetric flask. Add 400 mL of phosphate buffer, pH 8.0 (0.05 mol/L), TS, 50 mL of a solution of 10 mg of tetrabutylammonium hydrogen sulfate R per mL adjusted to pH 8.0 with sodium hydroxide (~80 g/L) TS and 20 mL of sodium edetate (20 g/L) TS adjusted to pH 8.0 with sodium hydroxide (~80 g/L) TS. Dilute to 1000 mL with water R.

Prepare the following solutions in hydrochloric acid (0.01 mol/L) VS immediately before use. For solution (1), use a quantity of the powered tablets sufficient to produce a solution containing the equivalent of 0.70 mg of doxycycline per mL. Solution (2), contains 0.80 mg of doxycycline hyclate RS per mL, solution (3) 0.80 mg of 6-epidoxycycline hydrochloride RS per mL, solution (4) 0.80 mg of metacycline hydrochloride RS per mL. For solution (5), mix 4.0 mL of solution (2) with 1.5 mL of solution (3) and 1.0 mL of solution (4) and dilute to 25 mL with hydrochloric acid (0.01 mol/L) VS and for solution (6), mix 2.0 mL of solution (3) and 2.0 mL of solution (4) and dilute to 100 mL with hydrochloric acid (0.01 mol/L) VS.

Operate with a flow rate of about 0.9 mL per minute. As a detector, use an ultraviolet spectrophotometer set at a wavelength of about 254 nm. Maintain the temperature of the column at 60 °C.

Inject 20 µL of solution (5). The assay is not valid unless the resolution between the first peak (metacycline) and the second peak (6-epidoxycycline) is greater than 1.25 and the resolution between the second peak and the third peak (doxycycline) is greater than 2.0. If necessary, adjust the *tert*-butanol R content in the mobile phase. The test is not valid unless the symmetry factor for the third peak is less than 1.25. Inject alternately 20 µL each of solutions (1) and (2).

Measure the areas of the peak responses obtained in the chromatograms from solutions (1) and (2) and calculate the content of doxycycline ($C_{22}H_{24}N_2O_8$) in the tablets, considering the declared content of $C_{22}H_{24}N_2O_8$ in doxycycline hyclate RS.

Impurities. The impurities limited by the requirements of this monograph include those listed in the monograph for Doxycycline hyclate.