Status: Effectivity information can only be shown for content published to the website.

Update information can only be shown for content published to the website.

Amitriptyline Tablets

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

EAG/Panel/Working Party	Medicinal Chemicals 3
Contact Details	adrian.evans@mhra.gov.uk
Deadline for Comment	31st March 2019
Target Publication Date (subject to change)	BP 2020
Notes:	Revised monograph: Identification, Dissolution, Related Substances and Assay If limits are too restrictive, please provide batch/stability data to demonstrate that an increase is required.

Action and use

Monoamine reuptake inhibitor; tricyclic antidepressant.

DEFINITION

Amitriptyline Tablets contain Amitriptyline Hydrochloride. They are coated.

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

Content of amitriptyline hydrochloride, $C_{20}H_{23}N,HCl$

90.0 to 110.0% of the stated amount.

IDENTIFICATION

A. Shake a quantity of the powdered tablets containing 20 mg of Amitriptyline Hydrochloride with 10 mL of *acetone*, filter and evaporate to dryness. The *infrared absorption spectrum* of the dried residue Appendix II A, is concordant with the *reference spectrum* of amitriptyline hydrochloride *(RS XXX)*.
B. In the Assay, the retention time fo the principal peak in the chrmatogram obtained with solution (1) is similar to that of the principal peak in the chromatogram obtained with solution (2).

TESTS

Dissolution

Comply with the requirements for Monographs of the British Pharmacopoeia in 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 0.1M hydrochloric acid, at a temperature of 37°, as the medium.

PROCEDURE

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

(1) After 45 minutes withdraw a sample of the medium and filter. Use the filtered medium, diluted with the dissolution medium if necessary, expected to contain 0.0011% w/v of Amitriptyline Hydrochloride.
(2) 0.0011% w/v of *amitriptyline hydrochloride BPCRS* in dissolution medium.
(3) 0.001% w/v each of *amitriptyline hydrochloride BPCRS* and *cyclobenzaprine hydrochloride BPCRS* in dissolution medium.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 4.6 mm) packed with *end-capped polar-embedded octadecylsilyl amorphous organosilica polymer* (5µm) (Waters X-Terra RP 18 is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 1.2 mL per minute.
(d) Use a column temperature of 40°.
(e) Use a detection wavelength of 220 nm.
(f) Inject 100 µL of each solution.

MOBILE PHASE

35 volumes of *acetonitrile* and 65 volumes of 0.523% w/v of *dipotassium hydrogen orthophosphate*, previously adjusted to pH 7.0 with *orthophosphoric acid*.

SYSTEM SUITABILITY

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

DETERMINATION OF CONTENT

Calculate the total content of $C_{20}H_{23}N$,HCl using the declared content of $C_{20}H_{23}N$,HCl in *amitriptyline hydrochloride BPCRS*.

Related substances

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

(1) Shake a quantity of the powdered tablets containing 50 mg of Amitriptyline Hydrochloride with 25 mL of the mobile phase, dilute to 50 mL, filter and use the filtrate.
(2) Dilute 1 volume of solution (1) to 200 volumes.
(3) 0.001% w/v of *amitriptyline hydrochloride BPCRS*, 0.001% w/v of *cyclobenzaprine hydrochloride BPCRS* and 0.00025% w/v of *dibenzosuberone BPCRS*.
(4) Dilute 1 volume of solution (2) to 5 volumes.

CHROMATOGRAPHIC CONDITIONS

The chromatographic procedure described under Dissolution may be used with an injection volume of 10 µL and a run time of 3 times the retention time of the peak due to amitriptyline in solution (1). When the chromatograms are recorded under the prescribed conditions the retention times relative to amitriptyline (retention time about 12 minutes) are; impurity B, about 0.9 and impurity A, about 2.7.

SYSTEM SUITABILITY

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

LIMITS

In the chromatogram obtained with solution (1):

the area of any peak corresponding to dibenzosuberone is not greater than the area of the peak due to dibenzosuberone in the chromatogram obtained with solution (3) (0.25%);

the area of any peak corresponding to cyclobenzaprine hydrochloride B is not greater than 0.2 times the area of the peak due to cyclobenzaprine hydrochloride in the chromatogram obtained with solution (3) (0.2%);

the area of any other secondary peak is not more than 0.4 times the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);

the sum of impurities is not greater than 0.5%;

Disregard any peak 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) *For film-coated tablets* Add 50 mL of *0.1M hydrochloric acid* to 20 tablets, shake vigorously until the tablets are completely disintegrated, add 100 mL of *methanol* and shake for 30 minutes. Dilute the suspension to 200 mL with *methanol*, centrifuge and dilute a volume of the supernatant liquid containing 25 mg of Amitriptyline Hydrochloride to 100 mL with *methanol (50%)*.
For sugar-coated tablets Shake a quantity of the powder containing 50 mg of Amitriptyline Hydrochloride with 50 mL of *0.1M hydrochloric acid* for 30 minutes, add 100 mL of *methanol* and shake for 30 minutes. Dilute the suspension to 200 mL with *water*, centrifuge and use the supernatant liquid.
(2) Dissolve 50 mg of *amitriptyline hydrochloride BPCRS* in 10 mL of *methanol* and dilute to 200 mL with *methanol (50%)*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (20 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (10 µm) (Nucleosil C18 is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 2 mL per minute.
(d) Use an ambient column temperature.
(e) Use a detection wavelength of 239 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

0.03M *sodium hexanesulfonate* in a mixture of equal volumes of *water* and *acetonitrile*, adjusted to pH 4.5 by the addition of *glacial acetic acid*,

DETERMINATION OF CONTENT

Calculate the content of $C_{20}H_{23}N,HCl$ using the declared content of $C_{20}H_{23}N,HCl$ in *amitriptyline hydrochloride BPCRS*.