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Loperamide Orodispersible Tablets

General Notices

Orodispersible Loperamide Tablets

Action and use

Opioid receptor agonist; antidiarrhoeal.

DEFINITION

Loperamide Orodispersible Tablets contain Loperamide Hydrochloride in a suitable orodispersible basis.

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

Content of loperamide hydrochloride, $C_{29}H_{33}ClN_2O_2,HCl$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.
(1) Shake a quantity of powdered tablets containing 10 mg of Loperamide Hydrochloride with 10 mL of *methanol* for 5 minutes and filter.
(2) 0.1% w/v of *loperamide hydrochloride BPCRS* in *methanol*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel F_{254}* (Merck silica gel 60 F_{254} plates are suitable).
(b) Use the mobile phase as described below.
(c) Apply 10 µL of each solution.
(d) Develop the plate to 15 cm.
(e) After removal of the plate, dry in air and examine under *ultraviolet light (254 nm)*.

MOBILE PHASE

2.5 volumes of *acetate buffer pH 4.7*, 17.5 volumes of *methanol*, 27 volumes of *ethyl acetate* and 53 volumes of *dichloromethane*.

CONFIRMATION

The principal spot in the chromatogram obtained with solution (1) corresponds in position and size to that in the chromatogram obtained with solution (2).

B. In the Assay, the retention time of the principal peak in the chromatogram obtained with solution (1) is similar to that of the principal peak in the chromatogram obtained with solution (2).

TESTS

Dissolution

Complies 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 500 mL of a buffer solution prepared by mixing 20 volumes of 1M *acetic acid* with 60 volumes of *water*, adjusting the pH to 4.7 with 1M *sodium hydroxide* and diluting to 100 volumes with *water*, at a temperature of 37°, as the medium.

PROCEDURE

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

0.005M *sodium octanesulfonate* containing, per 1000 mL, 1 mL of 13.5M *ammonia* and 0.5 mL of *triethylamine* and adjust the pH to 3.2 with *orthophosphoric acid* (solvent A).

(1) After 10 minutes withdraw a 10-mL sample of the medium and filter. Dilute the filtrate, if necessary, with dissolution medium to produce a solution containing 0.0004% w/v of Loperamide Hydrochloride.
(2) 0.0004% w/v of *loperamide hydrochloride BPCRS* in the dissolution medium.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 3.9 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (4 µm) (Novapak C18 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 an ambient column temperature.
(e) Use a detection wavelength of 226 nm.
(f) Inject 20 µL of each solution.

MOBILE PHASE

45 volumes of solvent A and 55 volumes of *acetonitrile*.

DETERMINATION OF CONTENT

Calculate the total content of loperamide hydrochloride, $C_{29}H_{33}ClN_2O_2$,HCl, in the medium from the chromatograms obtained and using the declared content of $C_{29}H_{33}ClN_2O_2$,HCl in *loperamide hydrochloride BPCRS*.

LIMITS

The amount of loperamide hydrochloride 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 freshly prepared solutions in solvent B.

35 volumes of 0.085M *potassium dihydrogen phosphate*, adjusted to pH 2.1 with *orthophosphoric acid*, and 65 volumes of *methanol* (solvent B).

(1) Shake a quantity of powdered tablets with a sufficient volume of solvent B to produce a solution containing 0.0035% w/v of Loperamide Hydrochloride. Filter and use the filtrate.
(2) Dilute 1 volume of solution (1) to 100 volumes.
(3) Dilute 1 volume to of solution (2) to 5 volumes.
(4) 0.0035% w/v of *loperamide hydrochloride BPCRS* and 0.000035% w/v of *loperamide N-oxide BPCRS* (impurity F).

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (7.5 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel* (5 µm) (Phenomenex Luna C18(2) is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 1 mL per minute.
(d) Use a column temperature of 30°.
(e) Use a detection wavelength of 219 nm.
(f) Inject 20 µL of each solution.
(g) For solution (1), allow the chromatography to proceed for 3 times the retention time of loperamide.

MOBILE PHASE

5 volumes of *tetrahydrofuran*, 37 volumes of *acetonitrile R1* and 58 volumes of a solution containing 0.46% w/v *ammonium dihydrogen phosphate* and 0.61% w/v *sodium decanesulfonate*, previously adjusted to pH 2.1 with *orthophosphoric acid*.

When the chromatograms are recorded under the prescribed conditions the retention time relative to loperamide (retention time about 15 minutes) is: impurity F, about 1.2.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (4), the *resolution* between the peaks due to loperamide and impurity F is at least 1.5.

LIMITS

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity F is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (1.0%);

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 any *secondary peaks*, excluding impurity F, is not greater the area of the principal peak in the chromatogram obtained with solution (2) (1.0%).

Disregard any peak with an area less than half the area of the principal peak in the chromatogram obtained with solution (3) (0.1%).

Uniformity of content

Tablets containing less than 2 mg and/or less than 2% w/w of Loperamide Hydrochloride comply with the requirements stated under Tablets using the following method of analysis. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Add 150 mL of *water* to one whole tablet and mix with the aid of ultrasound for 30 minutes, shake mechanically for 30 minutes and dilute with sufficient *acetonitrile* to produce a solution expected to contain 0.001% w/v of Loperamide Hydrochloride and filter.
(2) 0.001% w/v of *loperamide hydrochloride BPCRS* in a mixture of 45 volumes of *water* and 55 volumes of *acetonitrile*.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Dissolution may be used.

DETERMINATION OF CONTENT

Calculate the content of $C_{29}H_{33}ClN_2O_2$,HCl in each tablet using the declared content of $C_{29}H_{33}ClN_2O_2$,HCl in *loperamide hydrochloride BPCRS*.

ASSAY

For tablets containing less than 2 mg and/or less than 2% w/w of loperamide hydrochloride

Use the average of the 10 individual results obtained in the test for Uniformity of content.

For tablets containing 2 mg or more and 2% w/w or more of loperamide hydrochloride

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

(1) Mix a quantity of the powdered tablets containing 20 mg of Loperamide Hydrochloride with 90 mL of *water* with the aid of ultrasound for 10 minutes, shake for 30 minutes, dilute to 200 mL with *acetonitrile* and filter.
(2) 0.01% w/v of *loperamide hydrochloride BPCRS* in a mixture of 45 volumes of *water* and 55 volumes of *acetonitrile*.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Dissolution may be used.

DETERMINATION OF CONTENT

Calculate the content of $C_{29}H_{33}ClN_2O_2$,HCl in the tablets using the declared content of $C_{29}H_{33}ClN_2O_2$,HCl in *loperamide hydrochloride BPCRS*.

IMPURITIES

The impurities limited by the requirements of this monograph include impurity F listed under Loperamide Hydrochloride.