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Notes:	

Tolterodine Prolonged-release Capsules

Tolterodine Preparations

Action and use
Anticholinergic.

DEFINITION

Tolterodine Prolonged-release Capsules contain Tolterodine Tartrate. They are formulated so that the medicament is released over a period of several hours.

PRODUCTION

A suitable dissolution test is carried out to demonstrate the appropriate release of Tolterodine Tartrate. The dissolution profile reflects the in vivo performance which in turn is compatible with the dosage schedule recommended by the manufacturer.

The capsules comply with the requirements stated under Capsules and with the following requirements.

Content of tolterodine tartrate, $C_{26}H_{37}NO_7$
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 the contents of the capsules containing 12.5 mg of Tolterodine Tartrate with 5 mL of *methanol*, centrifuge and use the supernatant liquid.

(2) 0.25% w/v solution of *tolterodine tartrate 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 volumes of *triethylamine* 30 volumes of *ethyl acetate* and 70 volumes of n-*pentane*.

CONFIRMATION

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

B. In the Assay, the chromatogram obtained with solution (1) exhibits a peak with the same retention time as the principal peak in the chromatogram obtained with solution (2).

TESTS

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

(1) Shake a quantity of the contents of the capsules containing 10 mg of Tolterodine Tartrate with 7 mL of *methanol R1*, add sufficient *methanol R1* to produce 10mL and filter.

(2) Dilute 1 volume of solution (1) to 200 volumes with *methanol R1*.

(3) 0.02% w/v of *tolterodine tartrate BPCRS* and 0.004% w/v of *tolterodine impurity E EPCRS* in *methanol R1*.

(4) Dilute 1 volume of solution (2) to 5 volumes with *methanol R1*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column 25 cm × 4.6 mm packed with *base-deactivated end-capped octadecylsilyl silica gel for chromatography* (5 µm) (Hypersil BDS C18 is suitable).

(b) Use gradient 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 220 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

mobile phase A To 450 volumes of 0.288% w/v *ammonium dihydrogen orthophosphate* add 5 volumes of *triethylamine R2*. Adjust the mixture to pH 5.9 with a 50% v/v solution of *orthophosphoric acid* and add 550 volumes of *methanol R1*.

mobile phase B *methanol R1*.

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Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0 - 25	100	0	isocratic
25 - 45	100→80	0→20	linear gradient
45 - 46	80	20	isocratic
46 - 50	80→100	20→0	linear gradient
50 - 60	100	0	re-equilibration

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to impurity E and tolterodine tartrate is at least 1.5.

LIMITS

In the chromatogram obtained with solution (1):

the area of any *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.5%);

the sum of the areas of all *secondary peaks* is not greater than twice the area of the principal peak in the chromatogram obtained with solution (2) (1%).

Disregard any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (4) (0.1%).

Uniformity of content

Capsules containing less than 2 mg and/or less than 2% w/w of Tolterodine Tartrate comply with the requirements stated under Capsules using the following method of analysis.

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

(1) Shake the contents of one capsule insufficient *methanol R1* to obtain a solution containing 0.01% w/v of Tolterodine Tartrate and filter.

(2) 0.01% w/v of *tolterodine tartrate BPCRS* in *methanol R1*.

(3) 0.02% w/v of *tolterodine tartrate BPCRS* and 0.004% w/v of *tolterodine impurity E EPCRS* in *methanol R1*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column 25 cm × 4.6 mm packed with *base-deactivated end-capped octadecylsilyl silica gel for chromatography* (5 µm) (Hypersil BDS 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 220 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

To 450 volumes of 0.288% w/v *ammonium dihydrogen orthophosphate* add 5 volumes of *triethylamine R2*. Adjust the mixture to pH 5.9 with a 50% v/v solution of *orthophosphoric acid* and add 550 volumes of *methanol R1*.

SYSTEM SUITABILITY

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

DETERMINATION OF CONTENT

Calculate the total content of $C_{26}H_{37}NO_7$ in the capsules using the declared content of $C_{26}H_{37}NO_7$ in *tolterodine tartrate BPCRS*.

ASSAY

For capsules containing less than 2 mg and/or less than 2% w/w of Tolterodine Tartrate

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

For capsules containing 2 mg or more and 2% w/w or more of Tolterodine Tartrate

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

(1) Shake a quantity of the mixed contents of 20 capsules containing 10 mg of Tolterodine Tartrate with 80 mL of *methanol R1*, dilute to 100 mL with the same solvent and filter.

(2) 0.01% w/v of *tolterodine tartrate BPCRS* in *methanol R1*.

(3) 0.02% w/v of *tolterodine tartrate BPCRS* and 0.004% w/v of *tolterodine impurity E EPCRS* in *methanol R1*.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Uniformity of content may be used.

SYSTEM SUITABILITY

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

DETERMINATION OF CONTENT

Calculate the content of $C_{26}H_{37}NO_7$ in the capsules using the declared content of $C_{26}H_{37}NO_7$ in *tolterodine*

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Tolterodine Tartrate.