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Metronidazole Oral Suspension

General Notices

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

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Notes:	REVISED Acidity, Dissolution, Related Substances, Nitrite, and Assay updated. If limits are too restrictive, please provide batch/stability data to demonstrate that an increase is required.

Action and use

Imidazole antibacterial.

DEFINITION

Metronidazole Oral Suspension is a suspension of [Metronidazole Benzoate](#) in a suitable flavoured vehicle.
The oral suspension complies with the requirements stated under [Oral Liquids](#) and with the following requirements.

Content of metronidazole, C₆H₉N₃O₃

95.0 to 105.0% of the stated amount.

IDENTIFICATION

Mix a volume of the oral suspension containing the equivalent of 200 mg of Metronidazole with 20 mL of [water](#), filter under partial vacuum and wash the residue with three 10-mL quantities of [water](#)

(Whatman GF/C filter paper is suitable). Dissolve the residue as completely as possible in 10 mL of [acetone](#), filter and evaporate the filtrate to dryness. The [infrared absorption spectrum](#) of the residue after drying at 60°, [Appendix II A](#), is concordant with the *reference spectrum* of metronidazole benzoate ([RS 408](#)). Examine as discs prepared using potassium bromide.

TESTS

Acidity

pH, 4.7 to 6.7, [Appendix V L](#).

Dissolution

Comply 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 900 mL of 0.1M [hydrochloric acid](#), at a temperature of 37°, as the medium.

PROCEDURE

- (1) After 30 minutes withdraw a sample of the medium and measure the [absorbance](#) of the filtered sample, suitably diluted with [methanol](#) (50%) if necessary, to produce a solution expected to contain 0.002% w/v of Metronidazole Benzoate, at the maximum at 235 nm, [Appendix II B](#), using dissolution medium in the reference cell.
- (2) Measure the [absorbance](#) of a 0.002% w/v solution of [metronidazole benzoate BPCRS](#) in the dissolution medium using dissolution medium in the reference cell.

DETERMINATION OF CONTENT

Calculate the total content of Metronidazole, $C_6H_9N_3O_3$, in the medium from the absorbances obtained and using the declared content of $C_6H_9N_3O_3$ in [metronidazole benzoate BPCRS](#).

LIMITS

The amount of Metronidazole Benzoate released is not less than 80% (Q) of the stated amount.

Related substances

Carry out the method for [liquid chromatography](#), [Appendix III D](#), using the following solutions.

- (1) Disperse a suitable volume of the oral suspension with sufficient mobile phase B to produce a solution containing 1% w/v of Metronidazole Benzoate and filter (a 0.45- μ m nylon syringe filter is suitable).
- (2) Dilute 1 volume of solution (1) to 100 volumes in mobile phase B.

(3) 0.001% w/v of [metronidazole BPCRS](#), 0.001% w/v of [2-methyl-5-nitroimidazole BPCRS](#), and 0.001% w/v of [benzoic acid EPCRS](#) in mobile phase B.

(4) Dilute 1 volume of solution (2) to 20 volumes in mobile phase B.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with [di-isobutyloctadecylsilyl silica gel for chromatography](#) (5 µm) (Zorbax SB-C18 is suitable).

(b) Use gradient elution and the mobile phase described below.

(c) Use a flow rate of 1.0 mL per minute.

(d) Use an ambient column temperature.

(e) Use an autosampler temperature of 8°.

(f) Use a detection wavelength of 235 nm.

(g) Inject 10 µL of each solution.

MOBILE PHASE

Mobile phase A 30 volumes of [acetonitrile](#) and 70 volumes of 0.15% w/v solution of [potassium dihydrogen orthophosphate](#) adjusted to pH 3.2 with [orthophosphoric acid](#).

Mobile phase B 45 volumes of [acetonitrile](#) and 55 volumes of 0.15% w/v solution of [potassium dihydrogen orthophosphate](#) adjusted to pH 3.2 with [orthophosphoric acid](#).

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-10	100	0	isocratic
10-12	100→0	0→100	linear gradient
12-45	0	100	isocratic
45-46	0→100	100→0	linear gradient
46-50	100	0	re-equilibration

When the chromatograms are recorded under the prescribed conditions, the relative retention(s) with reference to Metronidazole Benzoate (retention time about 20 minutes) are: impurity A, about 0.23; impurity B, about 0.18 and impurity C, about 0.4.

SYSTEM SUITABILITY

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

LIMITS

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity B is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (1%);

the area of any [secondary peak](#) is not greater than 0.2 times the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);

the sum of the areas of any [secondary peaks](#) is not greater than 1.2 times the area of the principal peak in the chromatogram obtained with solution (2) (1.2%).

Disregard any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (4) (0.05%).

Nitrite

Mix a quantity of the oral suspension containing the equivalent of 1.0 g of Metronidazole Benzoate in sufficient [water](#) to produce 100 mL. To 40 mL of the solution add 2 mL of [sulfanilic acid solution](#), 2 mL of [aminonaphthalenesulfonic acid solution](#) and sufficient [water](#) to produce 50 mL. Allow to stand at room temperature for 1 hour. Measure the [absorbance](#) of the resulting solution at the maximum at 524 nm, [Appendix II B](#), using in the reference cell a solution prepared by treating 40 mL of [water](#) in the same manner, beginning at the words 'add 2 mL of [sulfanilic acid solution](#)...'.

The [absorbance](#) is not greater than that obtained by repeating the procedure using 1 mL of [nitrite standard solution \(20 ppm\)](#) diluted to 40 mL with [water](#) and treated at the same time and in the same manner, beginning at the words 'add 2 mL of [sulfanilic acid solution](#)...' (50 ppm, calculated with reference to the suspension).

ASSAY

Carry out the method for [liquid chromatography](#), [Appendix III D](#), using the following solutions.

- (1) Mix a weighed quantity of the oral suspension containing the equivalent of 200 mg of Metronidazole Benzoate in 150 mL of [methanol](#) (60%), add sufficient [water](#), with mixing and cooling, to produce 250 mL, mix and centrifuge. Further dilute 1 volume of this solution with 10 volumes of [methanol](#) (60%).
- (2) Dissolve 62.5 mg of [metronidazole benzoate BPCRS](#) in 1 mL of [dimethylformamide](#) and 30 mL of [methanol](#) and add sufficient [water](#), with mixing and cooling, to produce 50 mL. Dilute 1 volume to 10 volumes with [methanol](#) (60%).

CHROMATOGRAPHIC CONDITIONS

- (a) Use a stainless steel column (25 cm × 4.6 mm) packed with [octadecylsilyl silica gel for chromatography](#) (5 µm) (Spherisorb ODS 1 is suitable).
- (b) Use isocratic elution and the mobile phase described below.
- (c) Use a flow rate of 1.0 mL per minute.
- (d) Use an ambient column temperature .
- (e) Use a detection wavelength of 310 nm.
- (f) Inject 10 µL of each solution.

MOBILE PHASE

40 volumes of 1.25% w/v solution of [ammonium acetate](#), adjusted to pH 7.0 with [dilute acetic acid](#) or [dilute ammonia R1](#), as appropriate, and 60 volumes of [methanol](#) .

DETERMINATION OF CONTENT

Determine the weight per mL of the oral suspension, [Appendix V G](#), and calculate the content of $C_6H_9N_3O_3$, weight in volume, using the declared content of $C_6H_9N_3O_3$ in metronidazole benzoate BPCRS.

STORAGE

Metronidazole Oral Suspension should be protected from light.

LABELLING

The quantity of active ingredient is stated in terms of the equivalent amount of metronidazole.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Metronidazole Benzoate.

DRAFT MONOGRAPH
SUBJECT TO CHANGE