Edition: BP 2025 (Ph. Eur. 11.6 update)

Metformin Oral Solution

General Notices

Action and use

Biguanide; treatment of diabetes mellitus.

DEFINITION

Metformin Oral Solution is a solution of Metformin Hydrochloride in a suitable flavoured vehicle.

The oral solution complies with the requirements stated under Oral Liquids and with the following requirements.

Content of metformin hydrochloride, $C_4H_{11}N_5,HCl$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

In the Assay, record the UV spectrum of the principal peak in the chromatograms obtained with solutions (1) and (2) with a diode array detector in the range of 190 to 400 nm.

The UV spectrum of the principal peak in the chromatogram obtained with solution (1) is concordant with that of the peak in the chromatogram obtained with solution (2);

the retention time of the principal peak in the chromatogram obtained with solution (1) is similar to that of the 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) Dilute the oral solution with *methanol (40%)* to produce a solution containing 0.5% w/v of Metformin Hydrochloride and further dilute 1 volume of this solution to 10 volumes with mobile phase. Filter using a 0.45-µm PTFE or nylon filter if necessary.
(2) Dilute 1 volume of solution (1) to 100 volumes with the mobile phase and dilute 1 volume of the resulting solution to 10 volumes with the mobile phase.
(3) 0.00001% w/v of *metformin impurity A EPCRS* (1-cyanoguanidine) in the mobile phase.
(4) 0.05% w/v of *metformin for system suitability BPCRS* in the mobile phase.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 4.6 mm) packed with *end-capped dodecylsilyl silica gel for chromatography* (4 µm) (Phenomenex Synergi RP Max-RP 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 a column temperature of 35°.
(e) Use a detection wavelength of 218 nm.
(f) Inject 10 µL of each solution.

MOBILE PHASE

42 volumes of *methanol R2* and 58 volumes of a buffer solution containing 0.125% w/v of *sodium dodecyl sulfate*, 1% v/v of *triethylamine* and 1.46% w/v of *orthophosphoric acid* adjusted to pH 3.15 with *sodium hydroxide*.

When the chromatograms are recorded under the prescribed conditions, the relative retentions with reference to metformin (retention time about 10 minutes) are: impurity A, about 0.2; impurity D, about 0.5; impurity 1, about 1.1.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (4), the *resolution* between the peaks due to methylhydroxybenzoate and metformin hydrochloride is at least 1.5 and the *resolution* between the peaks due to metformin hydrochloride and metformin impurity 1 is at least 2.0.

LIMITS

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity 1 is not greater than three times the area of the principal peak in the chromatogram obtained with solution (2) (0.3%);

the area of any peak corresponding to metformin impurity A (1-cyanoguanidine) is not greater than the area of the principal peak in the chromatogram obtained with solution (3) (0.02%);

the area of any other *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.10%);

the sum of the areas of all *secondary peaks*, except those due to metformin impurity A (1-cyanoguanidine) and metformin impurity 1, is not greater than four times the area of the principal peak in the chromatogram obtained with solution (2) (0.4%);

Disregard any peak, except that due to metformin impurity A (1-cyanoguanidine), with an area less than half the area of the principal peak in the chromatogram obtained with solution (2) (0.05%).

ASSAY

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

Solution A: 1.7% w/v of *ammonium dihydrogen orthophosphate* adjusted to pH 3.0 with *orthophosphoric acid*.

Solution B: 1 volume of *acetonitrile R1* and 19 volumes of 0.1% v/v of *orthophosphoric acid*.

(1) Dilute a weighed quantity of the oral solution with sufficient volume of solution A to produce a solution containing 0.1% w/v of Metformin Hydrochloride and filter through a 0.45-µm nylon filter, if necessary. Dilute 1 volume of the resulting solution to 10 volumes with solution B.
(2) 0.01% w/v of *metformin hydrochloride BPCRS* in solution B.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (5 cm × 4.6 mm) packed with *strong cation-exchange silica gel for chromatography* (5 µm) (Phenomenex Luna SCX is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 2 mL per minute.
(d) Use a column temperature of 30°.
(e) Use a detection wavelength of 205 nm.
(f) Inject 20 µL of each solution.

MOBILE PHASE

16 volumes of *acetonitrile R1* and 84 volumes of 0.05M *potassium dihydrogen orthophosphate*, previously adjusted to pH 3.5 with *orthophosphoric acid* .

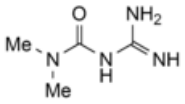
When the chromatograms are recorded under the prescribed conditions, the retention time of metformin is about 3 minutes.

DETERMINATION OF CONTENT

Determine the *weight per mL* of the oral solution, Appendix V G, and calculate the content of $C_4H_{11}N_5$,HCl, weight in volume, using the declared content of $C_4H_{11}N_5$,HCl in *metformin hydrochloride BPCRS*.

IMPURITIES

The impurities limited by the requirements of this monograph include impurities A and D listed under Metformin Hydrochloride and:



1. *N*′-(Aminoiminomethyl)-*N,N*-dimethylurea