Status: Currently Official on 14-Feb-2025
Official Date: Official as of 01-May-2020
Document Type: USP Monographs
DocId: GUID-0A807788-9987-4F83-BD1F-17A714489042_2_en-US
DOI: https://doi.org/10.31003/USPNF_M42420_02_01
DOI Ref: dhu9g

Irbesartan and Hydrochlorothiazide Tablets

DEFINITION

Irbesartan and Hydrochlorothiazide Tablets contain NLT 90.0% and NMT 110.0% of the labeled amounts of irbesartan ($C_{25}H_{28}N_6O$) and hydrochlorothiazide ($C_7H_8ClN_3O_4S_2$).

IDENTIFICATION

Change to read:

• **A.** ▲Spectroscopic Identification Tests ⟨197⟩, *Infrared Spectroscopy*: **197K**▲ (CN 1-May-2020)

Sample solution: Transfer the contents of 1 Tablet, previously crushed with a mortar and pestle, to a suitable vial. Add 5 mL of acetone, sonicate for 10 min, and pass through a membrane filter of 0.45-µm pore size. Evaporate the filtrate to dryness.

• **B.** The relative retention times of the major peaks from the *Sample solution* correspond to those of the *Standard solution*, as obtained in the *Assay*.

ASSAY

• **Procedure**

Buffer: Dissolve 1.36 g of monobasic potassium phosphate in 900 mL of water, add 2 mL of triethylamine, and adjust with phosphoric acid to a pH of 3.0 ± 0.1. Dilute further with water to 1 L.

Mobile phase: Acetonitrile, methanol, and *Buffer* (13:20:67)

Acidified water: Adjust with phosphoric acid (or sodium hydroxide, if necessary) to a pH of 2.0 ± 0.1.

Extraction solution: Methanol and *Acidified water* (7:3)

Irbesartan standard stock solution: Dissolve USP Irbesartan RS in a suitable volumetric flask in methanol (1/5 of the volume of the flask), and dilute with *Extraction solution* to prepare a 0.6 mg/mL solution. Sonicate for 2 min.

Hydrochlorothiazide standard stock solution: Dissolve USP Hydrochlorothiazide RS in methanol (1/20 of the volume of the flask), and dilute with *Extraction solution* to prepare a 0.1 mg/mL solution. Sonicate for 2 min.

Irbesartan related compound A standard stock solution: 0.1 mg/mL of USP Irbesartan Related Compound A RS in methanol. Sonicate for 2 min.

Benzothiadiazine related compound A standard stock solution: 0.05 mg/mL of USP Benzothiadiazine Related Compound A RS in methanol. Sonicate for 2 min.

Standard solution: 0.24 mg/mL of irbesartan and 0.02 mg/mL of hydrochlorothiazide from the *Irbesartan standard stock solution* and the *Hydrochlorothiazide standard stock solution* in the *Extraction solution*

System suitability solution: Prepare 0.05 mg/mL of USP Irbesartan RS, 0.005 mg/mL of USP Hydrochlorothiazide RS, 1.0 µg/mL of USP Irbesartan Related Compound A RS, and 3.0 µg/mL of USP Benzothiadiazine Related Compound A RS in the *Extraction solution* from the respective Standard stock solutions

Sample stock solution: 0.75 mg/mL of irbesartan from NLT 5 Tablets in a suitable volumetric flask. Add *Acidified water* up to 30% of the volume of the flask, and sonicate until the Tablets disintegrate. Add methanol to fill the flask up to 90% of the total volume. Sonicate for 5 min, and stir. Dilute with methanol to volume, and pass through a filter of 0.45-µm pore size.

Sample solution: 0.225 mg/mL of irbesartan in the *Extraction solution* from the *Sample stock solution*. [Note—The hydrochlorothiazide concentration may vary depending on the ratio of irbesartan to hydrochlorothiazide in the Tablet.]

Chromatographic system

(See *Chromatography ⟨621⟩, System Suitability*.)

Mode: LC

Detector: UV 220 nm

Column: 4.6-mm × 25-cm; 5-µm packing L10

Flow rate: 1.5 mL/min

Injection volume: 10 µL

System suitability

Samples: *Standard solution* and *System suitability solution*

Suitability requirements

Resolution: NLT 1.7 between irbesartan and irbesartan related compound A; NLT 1.7 between hydrochlorothiazide and benzothiadiazine related compound A, *System suitability solution*

Relative standard deviation: NMT 1.5% for both the irbesartan and hydrochlorothiazide peaks, *Standard solution*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of $C_{25}H_{28}N_6O$ and $C_7H_8ClN_3O_4S_2$ in the portion of Tablets taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times 100$$

r_U = peak area of irbesartan or hydrochlorothiazide from the *Sample solution*

r_S = peak area of irbesartan or hydrochlorothiazide from the *Standard solution*

C_S = concentration of USP Irbesartan RS or USP Hydrochlorothiazide RS in the *Standard solution* (mg/mL)

C_U = nominal concentration of irbesartan or hydrochlorothiazide in the *Sample solution* (mg/mL)

Acceptance criteria: 90.0%–110.0%

PERFORMANCE TESTS

• **Dissolution** ⟨711⟩

Medium: 0.1 N hydrochloric acid; 1000 mL

Apparatus 2: 50 rpm

Time: 30 min

pH 3.0 phosphate buffer: 1.36 g/L of monobasic potassium phosphate in water. Adjust with 10% phosphoric acid to a pH of 3.0 ± 0.1. This solution is stable for 3 months.

Mobile phase: *pH 3.0 phosphate buffer*, methanol, and acetonitrile (45:35:20)

Irbesartan standard stock solution: Transfer 50 mg of USP Irbesartan RS to a 100-mL volumetric flask. Add 15 mL of methanol, and sonicate for 5 min. Dilute with *Medium* to volume. This solution is stable for 14 days when stored at 4°.

Hydrochlorothiazide standard stock solution: Transfer 20 mg of USP Hydrochlorothiazide RS to a 200-mL volumetric flask. Add 5 mL of methanol, and sonicate for 5 min. Dilute with *Medium* to volume. This solution is stable for 14 days when stored at 4°.

Standard solution: Prepare on day of use dilutions of the *Irbesartan standard stock solution* and *Hydrochlorothiazide standard stock solution* in *Medium* as directed in the table below:

Label Claim of Irbesartan/ Hydrochlorothiazide (mg/Tablet)	Volume of the Irbesartan standard stock solution (mL)	Volume of the Hydrochlorothiazide standard stock solution (mL)	Final Volume (mL)
75/12.5	15	12.5	100
150/12.5	30	12.5	100
300/12.5	60	12.5	100
300/25	60	25.0	100

System suitability solution: Transfer 10 mg of USP Irbesartan Related Compound A RS to a 100-mL volumetric flask. Add 5 mL of methanol, and sonicate to dissolve. Dilute with *Medium* to volume. Transfer 10.0 mL of this solution, 5.0 mL of the *Irbesartan standard stock solution*, and 12.5 mL of the *Hydrochlorothiazide standard stock solution* to a 100-mL volumetric flask. Dilute with *Medium* to volume.

Sample solution: Pass a portion of the solution under test through a suitable filter of 0.45-µm pore size, discarding the first few mL.

Chromatographic system

(See *Chromatography* ⟨621⟩, *System Suitability*.)

Mode: LC

Detector: UV 272 nm

Column: 4.6-mm × 25-cm; 5-µm packing L10

Column temperature: 40°

Flow rate: 1.4 mL/min

Injection volume: 25 µL

System suitability

Samples: *Standard solution* and *System suitability solution*

Suitability requirements

Resolution: NLT 2.0 between irbesartan and irbesartan related compound A, *System suitability solution*

Relative standard deviation: NMT 2.0% for both the irbesartan and hydrochlorothiazide peaks, *Standard solution*

Calculate the percentage of irbesartan and hydrochlorothiazide dissolved:

$$\text{Result} = (r_U/r_S) \times (C_S/L) \times V \times 100$$

r_U = peak response for irbesartan or hydrochlorothiazide from the *Sample solution*

r_S = peak response for irbesartan or hydrochlorothiazide from the *Standard solution*

C_S = concentration of irbesartan or hydrochlorothiazide in the *Standard solution*

L = label claim for irbesartan or hydrochlorothiazide (mg/Tablet)

V = volume of *Medium* (mL), 1000

Tolerances: NLT 80% (*Q*) of the labeled amounts of irbesartan ($C_{25}H_{28}N_6O$) and hydrochlorothiazide ($C_7H_8ClN_3O_4S_2$) are dissolved.

• **Uniformity of Dosage Units ⟨905⟩:** Meet the requirements

IMPURITIES

Organic Impurities

• **Procedure**

Buffer, Mobile phase, Acidified water, Extraction solution, System suitability solution, Standard solution, Sample solution, Chromatographic system, and **System suitability:** Proceed as directed in the *Assay*.

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of irbesartan related compound A in the portion of Tablets taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times 100$$

r_U = peak response of irbesartan related compound A from the *Sample solution*

r_S = peak response of irbesartan from the *Standard solution*

C_S = concentration of USP Irbesartan RS in the *Standard solution* (mg/mL)

C_U = nominal concentration of irbesartan in the *Sample solution* (mg/mL)

Calculate the percentage of benzothiadiazine related compound A in the portion of Tablets taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times 1/F \times 100$$

r_U = peak response of benzothiadiazine related compound A from the *Sample solution*

r_S = peak response of hydrochlorothiazide from the *Standard solution*

C_S = concentration of USP Hydrochlorothiazide RS in the *Standard solution* (mg/mL)

C_U = nominal concentration of hydrochlorothiazide in the *Sample solution* (mg/mL)

F = relative response factor (see *Impurity Table 1*)

Calculate the percentage of any other individual impurity in the portion of Tablets taken:

$$\text{Result} = (r_U/r_T) \times 100$$

r_U = peak response of each other impurity in the *Sample solution*

r_T = sum of the peak responses excluding hydrochlorothiazide and benzothiadiazine related compound A from the *Sample solution*

Acceptance criteria

Individual impurities: See *Impurity Table 1*.

Total impurities: NMT 1.5% (sum of all the individual unknown impurities, irbesartan related compound A, and benzothiadiazine related compound A)

Impurity Table 1

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Benzothiadiazine related compound A	0.15	1.3	1.0

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Hydrochlorothiazide	0.18	—	—
Irbesartan related compound A	0.86	1.0	0.3
Irbesartan	1.00	—	—
Any other individual, unidentified impurity	—	1.0	0.2

ADDITIONAL REQUIREMENTS

- **Packaging and Storage:** Preserve in well-closed containers.
- **USP Reference Standards** ⟨11⟩

USP Hydrochlorothiazide RS

USP Irbesartan RS

USP Irbesartan Related Compound A RS

1-Pentanoylamino-cyclopentanecarboxylic acid [2'-(*1H*-tetrazol-5-yl)-biphenyl-4-ylmethyl]-amide.

$C_{25}H_{30}N_6O_2$ 446.54

USP Benzothiadiazine Related Compound A RS

4-Amino-6-chloro-1,3-benzenedisulfonamide.

$C_6H_8ClN_3O_4S_2$ 285.73

Auxiliary Information - Please check for your question in the FAQs before contacting USP.

Topic/Question	Contact	Expert Committee
IRBESARTAN AND HYDROCHLOROTHIAZIDE TABLETS	Documentary Standards Support	SM22020 Small Molecules 2

Chromatographic Database Information: Chromatographic Database

Most Recently Appeared In:
Pharmacopeial Forum: Volume No. PF 36(2)

Current DocID: GUID-0A807788-9987-4F83-BD1F-17A714489042_2_en-US

DOI: https://doi.org/10.31003/USPNF_M42420_02_01

DOI ref: dhu9g