Status: Currently Official on 16-Feb-2025
Official Date: Official as of 01-Dec-2017
Document Type: USP Monographs
DocId: GUID-9ED37694-507A-4D9C-A057-4904A602B495_1_en-US
DOI: https://doi.org/10.31003/USPNF_M53558_01_01
DOI Ref: gsg5f

Metoprolol Tartrate and Hydrochlorothiazide Tablets

DEFINITION

Metoprolol Tartrate and Hydrochlorothiazide Tablets contain NLT 90.0% and NMT 110.0% of the labeled amount of metoprolol tartrate $[(C_{15}H_{25}NO_3)_2 \cdot C_4H_6O_6]$ and hydrochlorothiazide ($C_7H_8ClN_3O_4S_2$).

IDENTIFICATION

• **A.** The retention times of the metoprolol and hydrochlorothiazide peaks of the *Sample solution* correspond to those of the *Standard solution*, as obtained in the *Assay*.

• **B.** The UV spectra of the metoprolol and hydrochlorothiazide peaks of the *Sample solution* correspond to those of the *Standard solution*, as obtained in the *Assay*.

ASSAY

• **Procedure**

Solution A: 4.1 g/L of monobasic sodium phosphate in water. Adjust with phosphoric acid to a pH of 3.0.

Solution B: Acetonitrile

Mobile phase: See *Table 1*.

Table 1

Time (min)	Solution A (%)	Solution B (%)
0.0	85	15
4.0	85	15
10.0	10	90
10.1	85	15
13	85	15

Diluent: Acetonitrile and *Solution A* (15:85)

Standard solution: 0.1 mg/mL of USP Metoprolol Tartrate RS and 0.05 mg/mL of USP Hydrochlorothiazide RS in *Diluent*

Sample solution: Nominally 0.1 mg/mL of metoprolol tartrate and 0.05 mg/mL of hydrochlorothiazide in *Diluent* prepared as follows. Transfer a portion of the powder from NLT 20 finely powdered Tablets to a suitable volumetric flask and dissolve in a suitable amount of *Diluent*. Sonication may be necessary for complete dissolution. Dilute with *Diluent* to volume.

Chromatographic system

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

Mode: LC

Detector: UV 223 nm. For *Identification B*, use a diode array detector in the range of 200–400 nm.

Column: 4.6-mm × 10-cm; 3.5-µm packing L1

Autosampler temperature: 4°

Flow rate: 1 mL/min

Injection volume: 10 µL

System suitability

Sample: *Standard solution*

[Note—The relative retention times for hydrochlorothiazide and metoprolol are 0.56 and 1.0, respectively.]

Suitability requirements

Tailing factor: NMT 2.0 for metoprolol and hydrochlorothiazide

Relative standard deviation: NMT 1.0% for metoprolol and hydrochlorothiazide

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of metoprolol tartrate $[(C_{15}H_{25}NO_3)_2 \cdot C_4H_6O_6]$ and hydrochlorothiazide ($C_7H_8ClN_3O_4S_2$) in the portion of Tablets taken:

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

r_U = peak response of metoprolol or hydrochlorothiazide from the *Sample solution*

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

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

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

Acceptance criteria: 90.0%–110.0% of the labeled amount of metoprolol tartrate $[(C_{15}H_{25}NO_3)_2 \cdot C_4H_6O_6]$ and hydrochlorothiazide ($C_7H_8ClN_3O_4S_2$)

PERFORMANCE TESTS

• **Dissolution ⟨711⟩**

Medium: Simulated gastric fluid TS (without enzyme); 900 mL

Apparatus 1: 100 rpm

Time: 30 min

Determination of dissolved metoprolol tartrate

Standard solution: 0.05 mg/mL of USP Metoprolol Tartrate RS in *Medium*

Sample solution: Remove 125 mL of the solution under test, allow to cool to room temperature, and filter, discarding the first 25 mL of the filtrate. [Note—Retain 30 mL of the remaining filtrate of the solution under test for the *Determination of dissolved hydrochlorothiazide*.] If necessary, prepare 0.05 mg/mL of metoprolol tartrate from the filtrate in fresh *Medium*.

Instrumental conditions

Mode: UV

Analytical wavelength: 276 nm

Cell: 2 cm

Blank: *Medium*

Analysis

Samples: *Standard solution, Sample solution*, and *Blank*

Transfer to separate separators 50.0 mL each of the *Standard solution*, *Sample solution*, and *Blank*. Add 10 mL of 2.5 N sodium hydroxide to each separator, and extract each with three 15-mL portions of chloroform, filtering the chloroform extracts through pledgets of chloroform-prerinsed glass wool into individual 50-mL volumetric flasks. Dilute the contents of each flask with chloroform to volume, and mix. Determine the absorbances of the solutions obtained.

Calculate the percentage of the labeled amount of metoprolol tartrate $[(C_{15}H_{25}NO_3)_2 \cdot C_4H_6O_6]$ dissolved:

$$\text{Result} = (A_U/A_S) \times C_S \times V \times D \times (100/L)$$

A_U = absorbance of the *Sample solution*

A_S = absorbance of the *Standard solution*

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

V = volume of *Medium*, 900 mL

D = dilution factor of the *Sample solution*

L = label claim (mg/Tablet)

Determination of dissolved hydrochlorothiazide

Standard solution: 0.03 mg/mL of USP Hydrochlorothiazide RS in *Medium*

Sample solution: Pass a portion of the filtrate retained from the *Determination of dissolved metoprolol tartrate* through a filter of 0.8-µm or finer pore size, and discard the first 5 mL of the filtrate. If necessary, prepare 0.03 mg/mL of hydrochlorothiazide in fresh *Medium*.

Instrumental conditions

Mode: UV

Analytical wavelength: 316 nm

Cell: 2 cm

Blank: *Medium*

Analysis

Samples: *Standard solution*, *Sample solution*, and *Blank*

Determine the absorbances of the *Standard solution* and the *Sample solution* at the wavelength of maximum absorbance. Calculate the percentage of hydrochlorothiazide ($C_7H_8ClN_3O_4S_2$) dissolved:

$$\text{Result} = (A_U/A_S) \times C_S \times V \times D \times (100/L)$$

A_U = absorbance of the *Sample solution*

A_S = absorbance of the *Standard solution*

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

V = volume of *Medium*, 900 mL

D = dilution factor of the *Sample solution*

L = label claim (mg/Tablet)

Tolerances: NLT 80% (Q) of the labeled amount of metoprolol tartrate [$(C_{15}H_{25}NO_3)_2 \cdot C_4H_6O_6$] and NLT 80% ($Q$) of the labeled amount of hydrochlorothiazide ($C_7H_8ClN_3O_4S_2$) is dissolved.

• **Uniformity of Dosage Units ⟨905⟩, *Content Uniformity*:** Meet the requirements with respect to metoprolol tartrate and hydrochlorothiazide

IMPURITIES

• **Organic Impurities**

Solution A: Dissolve 3.9 g of ammonium acetate in 810 mL of water. Add 2.0 mL of triethylamine, 10.0 mL of glacial acetic acid, and 3.0 mL of phosphoric acid. [Note—Adjust the solution to a pH of 3.7 if needed.]

Solution B: Acetonitrile and *Solution A* (70:30)

Mobile phase: See *Table 2*.

Table 2

Time (min)	Solution A (%)	Solution B (%)
0	90	10
15.0	80	20
30.0	40	60
40.0	40	60
40.1	90	10
45	90	10

Diluent: Acetonitrile and *Solution A* (17:83)

System suitability solution: 0.7 µg/mL of USP Maltol RS, 5 µg/mL of USP Benzothiadiazine Related Compound A RS, and 0.5 mg/mL of USP Hydrochlorothiazide RS in *Diluent*

Standard solution: 10.0 µg/mL of USP Metoprolol Tartrate RS and 2.5 µg/mL of USP Hydrochlorothiazide RS in *Diluent*

Sensitivity solution: 1.0 µg/mL of USP Metoprolol Tartrate RS and 0.25 µg/mL of USP Hydrochlorothiazide RS in *Diluent* from the *Standard solution*

Sample solution: Nominally 1 mg/mL of metoprolol tartrate in *Diluent* prepared as follows. Transfer a suitable portion of NLT 20 finely powdered Tablets, equivalent to 200 mg of metoprolol tartrate, into a suitable volumetric flask and add *Diluent* to about 50% of the flask volume. Sonicate for 20 min with occasional swirling. Stir for 15 min. Dilute with *Diluent* to volume. Centrifuge a portion of the solution. Use the supernatant.

Chromatographic system

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

Mode: LC

Detectors

Metoprolol and related impurities: UV 275 nm

Hydrochlorothiazide and related impurities: UV 320 nm

Column: 4.6-mm × 15-cm; 5-µm packing L1

Flow rate: 1 mL/min

Injection volume: 20 µL

System suitability

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

[NOTE—See *Table 3* for relative retention times.]

Suitability requirements

Resolution: NLT 1.5 between maltol and benzothiadiazine related compound A; NLT 3.0 between benzothiadiazine related compound A and hydrochlorothiazide, *System suitability solution*

Relative standard deviation: NMT 5.0% for metoprolol and hydrochlorothiazide, *Standard solution*

Signal-to-noise ratio: NLT 10 for metoprolol and hydrochlorothiazide, *Sensitivity solution*

Analysis

Samples: *Standard solution* and *Sample solution*

For impurities detected at UV 275 nm

Calculate the percentage of maltol and any unspecified degradation product (excluding the peaks that appear at 320 nm) 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 maltol or any unspecified degradation product from the *Sample solution*

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

C_S = concentration of USP Metoprolol Tartrate RS in the *Standard solution* (µg/mL)

C_U = nominal concentration of metoprolol tartrate in the *Sample solution* (µg/mL)

F = relative response factor (relative to metoprolol)

For impurities detected at UV 320 nm

Calculate the percentage of benzothiadiazine related compound A and any unspecified degradation product (excluding the peaks that appear at 275 nm) 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 or any unspecified degradation product 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* (µg/mL)

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

F = relative response factor (relative to hydrochlorothiazide)

Acceptance criteria: See *Table 3*. Disregard peaks below 0.1%.

Table 3

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Maltol	0.29	17	0.2
Benzothiadiazine related compound A[a]	0.31	1.0	1.0
Hydrochlorothiazide	0.46	—	—
Metoprolol	1.00	—	—
Any unspecified degradation product[b]	—	1.0	0.2
Total degradation products[c]	—	—	1.0

[a] Not to be included in the total degradation products.

[b] Based on the sum of unspecified degradation products determined at 275 nm and at 320 nm.

[c] Excluding benzothiadiazine related compound A.

ADDITIONAL REQUIREMENTS

• **Packaging and Storage:** Preserve in tight, light-resistant containers. Store at controlled room temperature.

• **USP Reference Standards** ⟨11⟩

USP Benzothiadiazine Related Compound A RS

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

$C_6H_8ClN_3O_4S_2$ 285.73

USP Hydrochlorothiazide RS

USP Maltol RS

3-Hydroxy-2-methyl-4-pyrone.

$C_6H_6O_3$ 126.11

USP Metoprolol Tartrate RS

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

Topic/Question	Contact	Expert Committee
METOPROLOL TARTRATE AND HYDROCHLOROTHIAZIDE TABLETS	Documentary Standards Support	SM22020 Small Molecules 2
REFERENCE STANDARD SUPPORT	RS Technical Services RSTECH@usp.org	SM22020 Small Molecules 2

Chromatographic Database Information: Chromatographic Database

Most Recently Appeared In:
Pharmacopeial Forum: Volume No. PF 42(4)

Current DocID: GUID-9ED37694-507A-4D9C-A057-4904A602B495_1_en-US

DOI: https://doi.org/10.31003/USPNF_M53558_01_01

DOI ref: gsg5f