Status: Currently Official on 15-Feb-2025
Official Date: Official as of 01-Aug-2023
Document Type: USP Monographs
DocId: GUID-3782C9D9-A9DE-4F93-A7B6-F602E17C606D_4_en-US
DOI: https://doi.org/10.31003/USPNF_M4632_04_01
DOI Ref: q9e1i

Montelukast Sodium Chewable Tablets

DEFINITION

Montelukast Sodium Chewable Tablets contain Montelukast Sodium equivalent to NLT 92.5% and NMT 107.5% of the labeled amount of montelukast ($C_{35}H_{36}ClNO_3S$).

[Note—Avoid exposure of samples containing montelukast to light.]

IDENTIFICATION

• **A. Spectroscopic Identification Tests ⟨197⟩, *Ultraviolet-Visible Spectroscopy*:** 197U

Diluent: Methanol and water (3:1)

Standard solution (for 4-mg Chewable Tablets): 0.026 mg/mL of USP Montelukast Dicyclohexylamine RS in *Diluent*

Standard solution (for 5-mg Chewable Tablets): 0.033 mg/mL of USP Montelukast Dicyclohexylamine RS in *Diluent*

Sample solution: Nominally (*L*/200) mg/mL of montelukast, where *L* is the label claim of montelukast in mg/Chewable Tablet prepared as follows. Transfer 1 Chewable Tablet to a suitable volumetric flask, add 25% of the flask volume of water, and let stand for 5–10 min until the Chewable Tablet has disintegrated. Add 55% of the flask volume of methanol, shake well, and sonicate for 70 min with occasional shaking. Cool to room temperature, dilute with methanol to volume, and mix well. Centrifuge a portion of the resulting solution to obtain a clear solution.

Wavelength range: 210–400 nm

Acceptance criteria: The *Sample solution* exhibits maxima only at the same wavelengths as the *Standard solution*.

• **B.** The retention time of the major peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay*.

ASSAY

• **Procedure**

Diluent: Methanol and water (3:1)

Solution A: 0.2% (v/v) Trifluoroacetic acid in water

Solution B: Methanol and acetonitrile (3:2)

Mobile phase: See *Table 1*.

Table 1

Time (min)	Solution A (%)	Solution B (%)
0	48	52
5	45	55
12	45	55
22	25	75
23	25	75
25	48	52
30	48	52

Standard solution: 0.33 mg/mL of USP Montelukast Dicyclohexylamine RS in *Diluent*

System suitability solution: Transfer 10 mL of the *Standard solution* to a clear 10-mL volumetric flask, add 4 µL of hydrogen peroxide, and mix well. Expose the flask for at least 4 h to ambient light or 10 min to a 4 klx cool white light. [Note—Montelukast is partially converted to the *cis*-isomer under these conditions.]

Sensitivity solution: 0.33 µg/mL of USP Montelukast Dicyclohexylamine RS in *Diluent* from the *Standard solution*

Sample solution (for 4-mg Chewable Tablets): Nominally 0.24 mg/mL of montelukast prepared as follows. Transfer 12 Chewable Tablets to a suitable volumetric flask, add 75% of the flask volume of *Diluent*, and shake vigorously for 60 min. Dilute with *Diluent* to volume. Pass a

portion of the resulting solution through a suitable filter of 0.45-µm pore size, discarding the first mL of filtrate. Use the filtrate.

Sample solution (for 5-mg Chewable Tablets): Nominally 0.25 mg/mL of montelukast prepared as follows. Transfer 10 Chewable Tablets to a suitable volumetric flask, add 75% of the flask volume of *Diluent*, and shake vigorously for 60 min. Dilute with *Diluent* to volume. Pass a portion of the resulting solution through a suitable filter of 0.45-µm pore size, discarding the first mL of filtrate. Use the filtrate.

Chromatographic system

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

Mode: LC

Detector: UV 255 nm

Columns

Guard: 3.0-mm × 4-mm; packing L11

Analytical: 4.6-mm × 10-cm; 3-µm packing L11

Column temperature: 50°

Flow rate: 1.5 mL/min

Injection volume: 20 µL

Run time: 2 times the retention time of montelukast

System suitability

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

[NOTE—The relative retention times for the *cis*-isomer and montelukast are about 0.92 and 1.0, respectively.]

Suitability requirements

Resolution: NLT 1.5 between the *cis*-isomer and montelukast, *System suitability solution*

Relative standard deviation: NMT 2% for five injections, *Standard solution*

Signal-to-noise ratio: NLT 10, *Sensitivity solution*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of montelukast ($C_{35}H_{36}ClNO_3S$) in the portion of Chewable Tablets taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times (M_{r1}/M_{r2}) \times 100$$

r_U = peak response from the *Sample solution*

r_S = peak response from the *Standard solution*

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

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

M_{r1} = molecular weight of montelukast, 586.18

M_{r2} = molecular weight of montelukast dicyclohexylamine, 767.50

Acceptance criteria: 92.5%–107.5%

PERFORMANCE TESTS

• **DISSOLUTION ⟨711⟩**

Test 1

Medium: 0.5% (w/v) Sodium dodecyl sulfate in water; 900 mL. Do not deaerate.

Apparatus 2: 50 rpm

Time: 20 min

Solution A: 0.2% (v/v) Trifluoroacetic acid in water

Solution B: 0.2% (v/v) Trifluoroacetic acid in acetonitrile

Mobile phase: *Solution A* and *Solution B* (1:1)

Standard stock solution (for 4-mg Chewable Tablets): 0.30 mg/mL of USP Montelukast Dicyclohexylamine RS in methanol (equivalent to 0.23 mg/mL of montelukast)

Standard stock solution (for 5-mg Chewable Tablets): 0.35 mg/mL of USP Montelukast Dicyclohexylamine RS in methanol (equivalent to 0.27 mg/mL of montelukast)

Standard solution: (*L*/900) mg/mL of montelukast in *Medium* from the *Standard stock solution*, where *L* is the label claim in mg/Chewable Tablet of montelukast

Sample solution: Pass a portion of the solution under test through a suitable filter or centrifuge to obtain a clear solution.

Chromatographic system

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

Mode: LC

Detector: UV 389 nm

Column: 3.0-mm × 10-cm; 5-µm packing L11

Column temperature: 50°

Flow rate: 0.9 mL/min

Injection volume: 50 µL

Run time: 1.5 times the retention time of montelukast

System suitability

Sample: *Standard solution*

Suitability requirements

Tailing factor: NMT 1.5

Relative standard deviation: NMT 2%

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of montelukast ($C_{35}H_{36}ClNO_3S$) dissolved:

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

r_U = peak response from the *Sample solution*

r_S = peak response from the *Standard solution*

C_S = concentration of montelukast in the *Standard solution* (mg/mL)

V = volume of *Medium*, 900 mL

L = label claim (mg/Chewable Tablet)

Tolerances: NLT 80% (Q) of the labeled amount of montelukast ($C_{35}H_{36}ClNO_3S$) is dissolved.

Test 2: If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 2*.

Medium: 0.5% (w/v) Sodium dodecyl sulfate in water; 900 mL

Apparatus 2: 50 rpm

Time: 45 min

Solution A: 0.07 g/L of monobasic sodium phosphate

Solution B: Acetonitrile

Mobile phase: *Solution A* and *Solution B* (45:55). Add 1.33 mL/L of triethylamine and adjust with phosphoric acid to a pH of 6.7.

Standard stock solution: 0.1 mg/mL of montelukast from montelukast sodium hydrate prepared as follows. Transfer a suitable amount of montelukast sodium hydrate to an appropriate volumetric flask. Dissolve in 4% of the flask volume of methanol and dilute with *Medium* to volume. Determine the water content of montelukast sodium hydrate at the time of use.

Standard solution: 0.005 mg/mL of montelukast in *Medium* from the *Standard stock solution*

Sample solution: Centrifuge a portion of the solution under test.

Chromatographic system

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

Mode: LC

Detector: UV 225 nm

Column: 4.6-mm × 5-cm; 1.8-µm packing L1

Column temperature: 35°

Flow rate: 1 mL/min

Injection volume: 100 µL

Run time: 1.5 times the retention time of montelukast

System suitability

Sample: *Standard solution*

Suitability requirements

Relative standard deviation: NMT 2.0%

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of montelukast ($C_{35}H_{36}ClNO_3S$) dissolved:

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

r_U = peak response from the *Sample solution*

r_S = peak response from the *Standard solution*

C_S = concentration of montelukast in the *Standard solution* (mg/mL)

V = volume of *Medium*, 900 mL

L = label claim (mg/Chewable Tablet)

Tolerances: NLT 70% (*Q*) of the labeled amount of montelukast ($C_{35}H_{36}ClNO_3S$) is dissolved.

Change to read:

• **Uniformity of Dosage Units ⟨905⟩:** ▲Meet the requirements▲ (CN 1-Aug-2023)

Procedure for content uniformity

Solution A, Solution B, Mobile phase, and **System suitability:** Proceed as directed in *Dissolution Test 1*.

Diluent: Methanol and water (3:1)

Standard solution (for 4-mg Chewable Tablets): 0.026 mg/mL of USP Montelukast Dicyclohexylamine RS in *Diluent*

Standard solution (for 5-mg Chewable Tablets): 0.033 mg/mL of USP Montelukast Dicyclohexylamine RS in *Diluent*

Sample solution: Nominally (*L*/200) mg/mL of montelukast, where *L* is the label claim of montelukast in mg/Chewable Tablet prepared as follows. Transfer 1 Chewable Tablet to a suitable volumetric flask, add 25% of the flask volume of water, and let stand for 5–10 min until the Chewable Tablet has disintegrated. Add 55% of the flask volume of methanol, shake well, and sonicate for 70 min with occasional shaking. Cool to room temperature, dilute with methanol to volume, and mix well. Pass a portion of the resulting solution through a suitable filter or centrifuge to obtain a clear solution.

Chromatographic system: Proceed as directed in *Dissolution Test 1*, except use an *Injection volume* of 10 µL.

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of montelukast ($C_{35}H_{36}ClNO_3S$) in the Chewable Tablet taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times (M_{r1}/M_{r2}) \times 100$$

r_U = peak response from the *Sample solution*

r_S = peak response from the *Standard solution*

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

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

M_{r1} = molecular weight of montelukast, 586.18

M_{r2} = molecular weight of montelukast dicyclohexylamine, 767.50

▲▲ (CN 1-Aug-2023)

IMPURITIES

• **Organic Impurities**

Diluent, Solution A, Solution B, Mobile phase, Standard solution, System suitability solution, Sensitivity 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 any individual degradation product in the portion of Chewable Tablets taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times (M_{r1}/M_{r2}) \times (1/F) \times 100$$

r_U = peak response of any individual degradation product from the *Sample solution*

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

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

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

M_{r1} = molecular weight of montelukast, 586.18

M_{r2} = molecular weight of montelukast dicyclohexylamine, 767.50

F = relative response factor (see *Table 2*)

Acceptance criteria: See *Table 2*. Disregard any peak with an area less than that of the *Sensitivity solution*.

Table 2

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Sulfoxide impurity[a,b]	0.45	1.0	1.5
Montelukast ketone impurity[c]	0.71	1.7	0.2
cis-Isomer[d]	0.92	1.0	0.3
Montelukast	1.0	—	—
Methylketone impurity[e,f]	1.04	—	—
Michael adduct 1[g,e]	1.16	—	—
Michael adduct 2[h,e]	1.18	—	—
Methylstyrene impurity[i,e]	1.55	—	—
Any other individual degradation product	—	1.0	0.2
Total impurities	—	—	2.0

[a] These two impurities are not resolved by the method and need to be integrated together to determine conformance.

[b] [1-[[[1-[3-[(*E*)-2-(7-Chloroquinolin-2-yl)ethenyl]phenyl]-3-[2-(1-hydroxy-1-methylethyl)phenyl]propyl]sulfinyl]methyl]cyclopropyl]acetic acid.

[c] (*E*)-1-{3-[2-(7-Chloroquinolin-2-yl)vinyl]phenyl}-3-[2-(2-hydroxypropan-2-yl)phenyl]propan-1-one.

[d] [1-[[[(1*R*)-1-[3-[(*Z*)-2-(7-Chloroquinolin-2-yl)ethenyl]phenyl]-3-[2-(1-hydroxy-1-methylethyl)phenyl]propyl]sulfanyl]methyl]cyclopropyl]acetic acid.

[e] This is a process impurity and is included in the table for identification only. This impurity is controlled in the drug substance. It is not to be reported for the drug product and should not be included in the total impurities.

[f] [1-[[[(1*R*)-3-(2-Acetylphenyl)-1-[3-[(*E*)-2-(7-chloroquinolin-2-yl)ethenyl]phenyl]propyl]sulfanyl]methyl]cyclopropyl]acetic acid.

[g] 1-[[[(1*R*)-1-[3-[(1*R*)-1-[[[1-(Carboxymethyl)cyclopropyl]methyl]sulfanyl]-2-(7-chloroquinolin-2-yl)ethyl]phenyl]-3-[2-(1-hydroxy-1-methylethyl)phenyl]propyl]sulfanyl]methyl]cyclopropyl]acetic acid.

[h] 1-[[[(1*R*)-1-[3-[(1*S*)-1-[[[1-(Carboxymethyl)cyclopropyl]methyl]sulfanyl]-2-(7-chloroquinolin-2-yl)ethyl]phenyl]-3-[2-(1-hydroxy-1-methylethyl)phenyl]propyl]sulfanyl]methyl]cyclopropyl]acetic acid.

[i] [1-[[[(1*R*)-1-[3-[(*E*)-2-(7-Chloroquinolin-2-yl)ethenyl]phenyl]-3-[2-(1-methylethenyl)phenyl]propyl]sulfanyl]methyl]cyclopropyl]acetic acid.

ADDITIONAL REQUIREMENTS

- **Packaging and Storage:** Preserve in tight containers, protected from light. Store at controlled room temperature.
- **Labeling:** When more than one *Dissolution* test is given, the labeling states the test used only if *Test 1* is not used.
- **USP Reference Standards** ⟨11⟩

USP Montelukast Dicyclohexylamine RS $C_{35}H_{36}ClNO_3S \cdot C_{12}H_{23}N$ 767.50

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

Topic/Question	Contact	Expert Committee
MONTELUKAST SODIUM CHEWABLE TABLETS	Documentary Standards Support	SM52020 Small Molecules 5

Chromatographic Database Information: Chromatographic Database

Most Recently Appeared In:
Pharmacopeial Forum: Volume No. PF 40(5)

Current DocID: GUID-3782C9D9-A9DE-4F93-A7B6-F602E17C606D_4_en-US

DOI: https://doi.org/10.31003/USPNF_M4632_04_01

DOI ref: q9e1i