Montelukast Sodium Tablets

Type of Posting	Revision Bulletin
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Expert Committee	Chemical Medicines Monographs 5
Reason for Revision	Compliance

In accordance with the Rules and Procedures of the Council of Experts, the Chemicals Medicines Monographs 5 Expert Committee has revised the Montelukast Sodium Tablets monograph. The purpose for the revision is to add two dissolution tests for generic products approved by the FDA.

- The liquid chromatographic procedure in *Dissolution Test 2* is based on analyses perfomed with a Zorbax Eclipse XDB brand of L1 column. The typical retention time for montelukast is about 10 min.

- The liquid chromatographic procedure in *Dissolution Test 3* is based on analyses perfomed with a Luna C18(2) brand of L1 column. The typical retention time for montelukast is about 3.5 min.

The Montelukast Sodium Tablets Revision Bulletin supersedes the monograph becoming official in *USP 39–NF 34*. The Revision Bulletin will be incorporated in the *Second Supplement* to *USP 39–NF 34*.

Should you have any questions, please contact Mary P. Koleck, Ph.D., Scientific Liaison (301-230-7420 or mpk@usp.org).

Add the following:

▲Montelukast Sodium Tablets

DEFINITION

Montelukast Sodium 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. ULTRAVIOLET ABSORPTION ⟨197U⟩**

  Diluent: Methanol and water (3:1)

  Standard solution: 0.026 mg/mL of USP Montelukast Dicyclohexylamine RS in *Diluent*

  Sample solution: Nominally 0.02 mg/mL of montelukast prepared as follows. Transfer one Tablet equivalent to 10 mg of montelukast to a suitable volumetric flask, add 25% of the flask volume of water, and let stand for 5–10 min until the Tablet has disintegrated. Add 60% 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: 0.52 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: 0.52 µg/mL of USP Montelukast Dicyclohexylamine RS in *Diluent* from the *Standard solution*

Sample solution: Nominally 0.4 mg/mL of montelukast prepared as follows. Transfer a number of Tablets equivalent to 100 mg of montelukast to a suitable volumetric flask, add 70% of the flask volume of *Diluent*, and sonicate for 30 min. Shake for 30 min on a platform shaker. Dilute with *Diluent* to volume and stir for 30 min. Pass a portion 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: 15 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 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

Change to read:

- **DISSOLUTION ⟨711⟩**

  •Test 1• (RB 1-May-2016)

  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: 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/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: 20 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/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 a suitable volumetric flask. Dissolve in 5% 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: 0.01 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/Tablet)

Tolerances: NLT 80% (*Q*) of the labeled amount of montelukast ($C_{35}H_{36}ClNO_3S$) is dissolved.
Test 3: If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 3*.
Medium: 0.5% (w/v) Sodium dodecyl sulfate in water; 900 mL
Apparatus 2: 50 rpm
Time: 30 min
Solution A: Acetonitrile and water (80:20)
Solution B: 3% Trifluoroacetic acid in *Solution A* prepared as follows. Transfer 3 mL of trifluoroacetic acid to a 100-mL volumetric flask and dilute with *Solution A* to volume.
Mobile phase: Acetonitrile, water, and *Solution B* (75: 25: 0.05).
Standard solution: (*L*/900) mg/mL of montelukast in *Medium* from montelukast sodium hydrate, where *L* is the label claim in mg/Tablet of montelukast. Determine the water content of montelukast sodium hydrate at the time of use.
Sample solution: Pass a portion of the solution under test through a suitable filter to obtain a clear solution.
Chromatographic system
(See *Chromatography* ⟨621⟩, *System Suitability*.)
Mode: LC
Detector: UV 346 nm
Column: 4.6-mm × 10-cm; 3-µm packingL1
Flow rate: 1.5 mL/min
Injection volume: 25 µL
Run time: NLT 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/Tablet)

Tolerances: NLT 80% (*Q*) of the labeled amount of montelukast ($C_{35}H_{36}ClNO_3S$) is dissolved.● (RB 1-May-2016)

Change to read:

• **Uniformity of Dosage Units** ⟨905⟩
Procedure for content uniformity
Solution A, Solution B, Mobile phase, and **System suitability:** Proceed as directed in *Dissolution* •*Test 1*.● (RB 1-May-2016)
Diluent: Methanol and water (3:1)
Standard solution: 0.052 mg/mL of USP Montelukast Dicyclohexylamine RS in *Diluent*
Sample solution: Nominally 0.04 mg/mL of montelukast prepared as follows. Transfer one Tablet equivalent to 10 mg of montelukast to a suitable volumetric flask, add 25% of the flask volume of water,

and let stand for 5–10 min until the Tablet has disintegrated. Add 60% 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*,• (RB 1-May-2016) 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 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

Acceptance criteria: Meet the requirements

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 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	2.0
Montelukast ketone impurity[c]	0.71	1.7	0.2
cis-Isomer[d]	0.92	1.0	0.2
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	—	—	3.0

[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.

Add the following:

••**LABELING** When more than one *Dissolution* test is given, the labeling states the test used only if *Test 1* is not used.• (RB 1-May-2016)

• **USP REFERENCE STANDARDS** ⟨**11**⟩

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

▲*USP39*