# Montelukast Sodium Oral Granules

## DEFINITION

Montelukast Sodium Oral Granules contain Montelukast Sodium equivalent to NLT 90.0% and NMT 108.0% 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:** 3.3 µg/mL of USP Montelukast Dicyclohexylamine RS in *Diluent*

**Sample stock solution:** Nominally 0.02 mg/mL of montelukast prepared as follows. Transfer the contents of one packet to a suitable volumetric flask, add 66% of the flask volume of *Diluent*, shake well, and sonicate for 15 min with occasional shaking. Cool to room temperature, dilute with *Diluent* to volume, and mix well.

**Sample solution:** Nominally 2 µg/mL of montelukast in *Diluent* from the *Sample stock solution*. Pass a portion of the resulting solution through a suitable filter of 0.45-µm pore size or centrifuge 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:** Nominally 0.24 mg/mL of montelukast prepared as follows. Transfer the equivalent of 60 mg of montelukast from the contents of the packets (NLT 15) to a 500-mL volumetric flask, and add 250 mL of *Diluent*. Shake well and sonicate for 30 min, with

occasional shaking. Pass a portion of the resulting solution through a suitable filter of 0.45-μm pore size or centrifuge to obtain a clear solution.

**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 2.0% 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 Oral Granules 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:** 90.0%−108.0%

**PERFORMANCE TESTS**
• **DISSOLUTION ⟨711⟩**
  **Test 1**
    **Medium:** 0.5% (w/v) sodium dodecyl sulfate in water; 900 mL. Do not deaerate.
    **Apparatus 1:** 100 mesh; 50 rpm
    **Time:** 15 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:** 0.33 mg/mL of USP Montelukast Dicyclohexylamine RS in methanol (equivalent to 0.25 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/packet of montelukast
    **Sample solution:** Place the entire contents of one packet in the basket. At the appropriate time point, pass a portion of the solution under test through a suitable filter to obtain a clear solution. Discard the first 10 mL of the filtrate.
    **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:** 25 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 2.0%

**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 of montelukast from the *Sample solution*

$r_S$ = peak response of montelukast 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/packet)

**Tolerances:** NLT 85% (*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 1:** 100 mesh; 50 rpm

**Time:** 15 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:** 0.004 mg/mL of montelukast in *Medium* from the *Standard stock solution*

**Sample solution:** Place the entire contents of one packet in the basket. At the appropriate time point, 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/packet)

**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:** 10 min

**Solution A:** 2.72 g/L of monobasic potassium phosphate in water

**Mobile phase:** Acetonitrile and *Solution A* (70:30)

**Diluent:** Acetonitrile and water (50:50)

**System suitability solution:** Expose a portion of *Standard solution* in a clear glass vial to direct room light for about 30 min.

**Standard stock solution:** 0.524 mg/mL of USP Montelukast Dicyclohexylamine RS in *Diluent* (equivalent to 0.4 mg/mL of montelukast)

**Standard solution:** 0.0065 mg/mL of USP Montelukast Dicyclohexylamine RS in *Medium* from the *Standard stock solution* (equivalent to 0.005 mg/mL of montelukast)

**Sample solution:** Transfer the entire contents of one packet to the dissolution vessel. At the specified time point, withdraw 10 mL of sample from the dissolution vessel. Pass a portion of the solution under test through a suitable filter. Discard the first 5 mL of the filtrate.

**Chromatographic system**

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

**Mode:** LC

**Detector:** UV 281 nm

**Column:** 4.6-mm × 3-cm; 3-µm packing L1

**Column temperature:** 40°

**Flow rate:** 0.8 mL/min

**Injection volume:** 25 µL

**Run time:** About 1.5 times the retention time of montelukast

**System suitability**

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

[NOTE—The relative retention times for *Z*-isomer and montelukast are 0.8 and 1.0, respectively.]

**Suitability requirements**

**Resolution:** NLT 2.0 between the *Z*-isomer and montelukast, *System suitability solution*

**Tailing factor:** NMT 2.0 for montelukast, *System suitability solution*

**Relative standard deviation:** NMT 2.0%, *Standard solution*

**Analysis**

**Samples:** *Standard solution* and *Sample solution*

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

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

$r_U$ = 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)

$V$ = volume of *Medium*, 900 mL

$L$ = label claim (mg/packet)

$M_{r1}$ = molecular weight of montelukast, 586.18

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

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

**Test 4:** If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 4*.

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

**Apparatus 1:** 100 mesh; 50 rpm

**Time:** 20 min

**Solution A:** 3.9 g/L of sodium phosphate monobasic dihydrate in water. Adjust with dilute phosphoric acid to a pH of 3.7.

**Mobile phase:** Acetonitrile and *Solution A* (80:20)

**Diluent:** *Medium*

**Standard solution:** 0.005 mg/mL of montelukast in *Diluent* from montelukast sodium hydrate. Determine the water content of montelukast sodium hydrate at the time of use.

**Sample solution:** Place the entire contents of one packet in the basket. At the specified time point, withdraw 10 mL of sample from the dissolution vessel. Pass a portion of the solution under test through a suitable filter paper. Discard the first 3 mL of the filtrate.

**Chromatographic system**

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

**Mode:** LC

**Detector:** UV 254 nm

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

**Temperatures**

    **Autosampler:** 20°

    **Column:** 28°

**Flow rate:** 1.5 mL/min

**Injection volume:** 50 µL

**Run time:** NLT 1.5 times the retention time of montelukast

**System suitability**

**Sample:** *Standard solution*

**Suitability requirements**

    **Tailing factor:** NMT 2.0 for montelukast

    **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:

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

$r_U$ = 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/packet)

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

*Change to read:*

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**Procedure for content uniformity**

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

**Standard solution:** 26.4 µg/mL of USP Montelukast Dicyclohexylamine RS in methanol

**Sample solution:** Nominally 0.02 mg/mL of montelukast prepared as follows. Transfer the contents of one packet to a suitable volumetric flask, add 66% of the flask volume of methanol, shake well, and sonicate for 15 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 of 0.45-µm pore size or centrifuge to obtain a clear solution.

**Chromatographic system:** Proceed as directed in *DissolutionTest 1*, except use an *Injection volume* of 5 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 packet taken:

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

$r_U$ = 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**

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**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 Oral Granules taken:

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

$r_U$ = 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 | 1.0 |
| 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[j,e] | 1.55 | — | — |
| Any other individual degradation product | — | 1.0 | 0.2 |
| Total impurities | — | — | 1.5 |

[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-{[(*R*)-1-(3-[(*R*)-1-{[1-(Carboxymethyl)cyclopropyl]methylthio}-2-(7-chloroquinolin-2-yl)ethyl]phenyl)-3-[2-(2-hydroxypropan-2-yl)phenyl]propylthio]methyl}cyclopropyl)acetic acid.

[h]   (1-{[(*R*)-1-(3-[(*S*)-1-{[1-(Carboxymethyl)cyclopropyl]methylthio}-2-(7-chloroquinolin-2-yl)ethyl]phenyl)-3-[2-(2-hydroxypropan-2-yl)phenyl]propylthio]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

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

| Topic/Question | Contact | Expert Committee |
|---|---|---|
| MONTELUKAST SODIUM ORAL GRANULES | Documentary Standards Support | SM52020 Small Molecules 5 |

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**Chromatographic Database Information:**   Chromatographic Database

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