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# Felodipine Extended-Release Tablets

## DEFINITION

Felodipine Extended-Release Tablets contain NLT 90.0% and NMT 110.0% of the labeled amount of felodipine ($C_{18}H_{19}Cl_2NO_4$).

## IDENTIFICATION

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

## ASSAY

- **Procedure**

**Buffer solution:** 6.9 mg/mL of monobasic sodium phosphate in water. Adjust with 1 M phosphoric acid to a pH of 3.0 ± 0.05.

**Mobile phase:** Acetonitrile, methanol, and *Buffer solution* (40:20:40)

**Standard stock solution:** 2 mg/mL of USP Felodipine RS in methanol. Sonication may be necessary for complete dissolution.

**Standard solution:** 0.02 mg/mL of USP Felodipine RS from the *Standard stock solution* in *Mobile phase*

**Sample stock solution:** Nominally 0.1 mg/mL of felodipine prepared as follows. Dissolve a quantity equivalent to 10 mg of felodipine from powdered Tablets (NLT 10) in 40 mL of acetonitrile and 20 mL of methanol in a 100-mL volumetric flask, and sonicate for 5 min. Add about 30 mL of *Buffer solution*, and shake by mechanical means for 30 min. Allow the solution to cool to room temperature, and dilute with *Buffer solution* to volume. Centrifuge a portion of the solution at high speed for 15 min.

**Sample solution:** Nominally 0.02 mg/mL of felodipine prepared as follows. Transfer 10 mL of the supernatant from the *Sample stock solution* to a 50-mL volumetric flask, and dilute with *Mobile phase* to volume. Pass a portion of this solution through a filter of 0.5-µm or finer pore size, discarding the first 4 mL of the filtrate.

**Chromatographic system**

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

**Mode:** LC

**Detector:** UV 362 nm. For *Identification B*, use a diode array detector in the range of 210–400 nm.

**Column:** 4.6-mm × 15-cm; 4-µm packing L1

**Flow rate:** 1 mL/min

**Injection volume:** 40 µL

**Run time:** NLT 2 times the retention time of felodipine

**System suitability**

**Sample:** *Standard solution*

**Suitability requirements**

**Tailing factor:** NMT 2.0

**Relative standard deviation:** NMT 2.0%

**Analysis**

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

Calculate the percentage of the labeled amount of felodipine ($C_{18}H_{19}Cl_2NO_4$) in the portion of Tablets taken:

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

$r_U$ = peak response of felodipine from the *Sample solution*

$r_S$ = peak response of felodipine from the *Standard solution*

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

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

**Acceptance criteria:** 90.0%–110.0%

## PERFORMANCE TESTS

***Change to read:***

- **Dissolution ⟨711⟩**

**Test 1**

**Medium:** pH 6.5 phosphate buffer with 1% sodium lauryl sulfate (Transfer 206 mL of 1 M ▲monobasic sodium phosphate,▲ (USP 1-Aug-2022) 196 mL of 0.5 M dibasic sodium phosphate anhydrous, and 50.0 g of sodium lauryl sulfate to a 5000-mL volumetric flask. Add about 4000 mL of water, and mix well. If necessary, adjust with 1 N sodium hydroxide to a pH of 6.5. Dilute with water to volume); 500 mL

**Apparatus 2:** 50 rpm, ▲with stationary basket. See ⟨711⟩, *Figures 2b* and *2c*.▲ (USP 1-Aug-2022)

**Times:** 2, 6, and 10 h

**Buffer solution:** ▲Prepare as directed for *Assay*.▲ (USP 1-Aug-2022)

**Mobile phase:** Acetonitrile, methanol, and *Buffer solution* (25:10:20)

**Standard stock solution:** 0.25 mg/mL of USP Felodipine RS in alcohol

**Standard solution:** (0.6 *L*/500) mg/mL of USP Felodipine RS from the *Standard stock solution* in *Medium*, where *L* is the label claim in mg/Tablet

**Sample solution:** ▲▲ (USP 1-Aug-2022) Pass a 10-mL portion of the solution under test, obtained at each time interval, through a suitable filter. ▲▲ (USP 1-Aug-2022)

**Chromatographic system:** Proceed as directed in the *Assay*, except for the *Injection volume*.

**Injection volume:** 100 µL

**Analysis**

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

Calculate the concentration ($C_i$) of felodipine ($C_{18}H_{19}Cl_2NO_4$) in the sample withdrawn from the vessel at each time point (*i*):

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

$r_U$ = peak response of felodipine from the *Sample solution* at each time point, *i*

$r_S$ = peak response of felodipine from the *Standard solution*

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

Calculate the percentage of the labeled amount of felodipine ($C_{18}H_{19}Cl_2NO_4$) dissolved at each time point (*i*):

$$\text{Result}_1 = C_1 \times V \times (1/L) \times 100$$

$$\text{Result}_2 = \{[C_2 \times (V - V_S)] + (C_1 \times V_S)\} \times (1/L) \times 100$$

$$\text{Result}_3 = (\{C_3 \times [V - (2 \times V_S)]\} + [(C_2 + C_1) \times V_S]) \times (1/L) \times 100$$

$C_i$ = concentration of felodipine in the *Sample solution* at the specified time point (mg/mL)

$V$ = volume of *Medium*, 500 mL

$L$ = label claim (mg/Tablet)

$V_S$ = volume of the *Sample solution* withdrawn at each time point, *i* (mL)

**Tolerances:** See *Table 1*.

**Table 1**

| Time Point (*i*) | Time (h) | Amount Dissolved (%) |
|---|---|---|
| 1 | 2 | 10–30 |
| 2 | 6 | 42–68 |
| 3 | 10 | NLT 75 |

The percentages of the labeled amount of felodipine ($C_{18}H_{19}Cl_2NO_4$) dissolved at the times specified conform to *Dissolution* ⟨711⟩, *Acceptance Table 2*.

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

**Medium:** 1% (w/v) polysorbate 80▲in water▲ (USP 1-Aug-2022); 500 mL

**Apparatus 1:** 100 rpm

**Times:** 1, 4, and 8 h

**Buffer solution:** Dissolve 6.9 g of monobasic sodium phosphate in 400 mL of water, add 8.0 mL of 1 M phosphoric acid, and dilute with water to 1000 mL.

**Mobile phase:** Acetonitrile, methanol, and *Buffer solution* (40:20:40)

**Standard stock solution:** 0.2 mg/mL of USP Felodipine RS in methanol. Sonicate for 2 min, cool, and dilute with methanol to final concentration.

**Standard solution:** (*L*/500) mg/mL of USP Felodipine RS in *Medium*, from the *Standard stock solution*, where *L* is the label claim in mg/Tablet

**Sample solution:** Pass a portion of the solution under test through a suitable filter of 0.45-µm pore size. Replace the withdrawn amount with *Medium*.

**Chromatographic system**

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

**Mode:** LC

**Detector:** UV 254 nm

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

**Flow rate:** 1 mL/min

**Injection volume:** 20 µL

▲**Run time:** NLT 2.5 times the retention time of felodipine▲ (USP 1-Aug-2022)

**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 concentration ($C_i$) of felodipine ($C_{18}H_{19}Cl_2NO_4$) in the sample withdrawn from the vessel at each time point (*i*):

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

$r_U$ = peak response of felodipine from the *Sample solution* at each time point, *i*

$r_S$ = peak response of felodipine from the *Standard solution*

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

Calculate the percentage of the labeled amount of felodipine ($C_{18}H_{19}Cl_2NO_4$) dissolved at each time point (*i*):

$$\text{Result}_1 = C_1 \times V \times (1/L) \times 100$$

$$\text{Result}_2 = [(C_2 \times V) + (C_1 \times V_S)] \times (1/L) \times 100$$

$$\text{Result}_3 = \{(C_3 \times V) + [(C_2 + C_1) \times V_S]\} \times (1/L) \times 100$$

$C_i$ = concentration of felodipine in the *Sample solution* at the specified time point (mg/mL)

$V$ = volume of *Medium*, 500 mL

$L$ = label claim (mg/Tablet)

$V_S$ = volume of the *Sample solution* withdrawn at each time point, *i* (mL)

**Tolerances:** See *Table 2*.

**Table 2**

| Time Point (*i*) | Time (h) | Amount Dissolved (%) |
|---|---|---|
| 1 | 1 | 5–30 |
| 2 | 4 | 45–70 |
| 3 | 8 | NLT 80 |

The percentages of the labeled amount of felodipine ($C_{18}H_{19}Cl_2NO_4$) dissolved at the times specified conform to *Dissolution* ⟨711⟩, *Acceptance Table 2*.

**Test 3:** If the product complies with this test, the labeling indicates that the product meets USP *Dissolution Test 3*.

**Medium:** pH 6.5 phosphate buffer with 1% sodium lauryl sulfate prepared as follows. 5.7 g/L of ▲monobasic sodium phosphate,▲ (USP 1-Aug-2022) 2.8 g/L of dibasic sodium phosphate, and 10 g/L of sodium lauryl sulfate in water, adjusted, if necessary, with diluted sodium hydroxide to a pH of 6.5 ± 0.05; 500 mL

**Apparatus 2:** 50 rpm, ▲with stationary basket. See ⟨711⟩, *Figures 2b* and *2c*.▲ (USP 1-Aug-2022)

**Times:** 2, 6, and 10 h

**Buffer solution:** 6.9 g/L of ▲monobasic sodium phosphate▲ (USP 1-Aug-2022) in water. Adjust with phosphoric acid to a pH of 3.0 ± 0.05.

**Mobile phase:** Acetonitrile, methanol, and *Buffer solution* (45:25:30)

**Standard stock solution:** 0.5 mg/mL of USP Felodipine RS in methanol. Sonication may be necessary for complete dissolution.

**Standard solution:** 0.01 mg/mL of USP Felodipine RS from the *Standard stock solution* in *Medium*. ▲▲ (USP 1-Aug-2022)

**Sample solution:** ▲▲ (USP 1-Aug-2022) Pass a portion of the solution under test, obtained at each time interval, through a suitable filter, discarding the first few milliliters.

**Chromatographic system**

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

**Mode:** LC

**Detector:** UV 362 nm

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

**Flow rate:** 2.0 mL/min

**Injection volume:** 40 µL

▲**Run time:** NLT 1.7 times the retention time of felodipine▲ (USP 1-Aug-2022)

**System suitability**

**Sample:** *Standard solution*

**Suitability requirements**

**Column efficiency:** NLT 1500 theoretical plates

**Relative standard deviation:** NMT 2.0%

**Analysis**

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

Calculate the concentration ($C_i$) of felodipine ($C_{18}H_{19}Cl_2NO_4$) in the sample withdrawn from the vessel at each time point ($i$):

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

$r_U$ = peak response of felodipine from the *Sample solution* at each time point, $i$

$r_S$ = peak response of felodipine from the *Standard solution*

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

Calculate the percentage of the labeled amount of felodipine ($C_{18}H_{19}Cl_2NO_4$) dissolved at each time point ($i$):

$$\text{Result}_1 = C_1 \times V \times (1/L) \times 100$$

$$\text{Result}_2 = \{[C_2 \times (V - V_S)] + (C_1 \times V_S)\} \times (1/L) \times 100$$

$$\text{Result}_3 = (\{C_3 \times [V - (2 \times V_S)]\} + [(C_2 + C_1) \times V_S]) \times (1/L) \times 100$$

$C_i$ = concentration of felodipine in the *Sample solution* at the specified time point (mg/mL)

$V$ = volume of *Medium*, 500 mL

$L$ = label claim (mg/Tablet)

$V_S$ = volume of the *Sample solution* withdrawn at each time point, $i$ (mL)

**Tolerances:** See *Table 3*.

**Table 3**

| Time Point (*i*) | Time (h) | Amount Dissolved (%) |
|---|---|---|
| 1 | 2 | 10–30 |
| 2 | 6 | 50–80 |
| 3 | 10 | NLT 80 |

The percentages of the labeled amount of felodipine ($C_{18}H_{19}Cl_2NO_4$) dissolved at the times specified conform to *Dissolution* ⟨711⟩, *Acceptance Table 2*.

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

**IMPURITIES**

***Change to read:***

• **Organic Impurities**

**Buffer solution** and **Mobile phase:** Prepare as directed in the *Assay*.

**Standard stock solution:** 150 µg/mL each of USP Felodipine RS and USP Felodipine Related Compound A RS in methanol. Sonication may be necessary for complete dissolution.

**Standard solution:** 1.5 µg/mL each of USP Felodipine RS and USP Felodipine Related Compound A RS from the *Standard stock solution* in *Mobile phase*

**Sensitivity solution:** 0.075 µg/mL each of USP Felodipine RS and USP Felodipine Related Compound A RS from the *Standard solution* in *Mobile phase*

**Sample solution:** Nominally 150 µg/mL of felodipine prepared as follows. Dissolve a quantity equivalent to 30 mg of felodipine from powdered Tablets (NLT 20) in a 200-mL volumetric flask. Add 80 mL of acetonitrile and 40 mL of methanol, and sonicate for 15 min. Add about 60 mL of *Buffer solution*, and stir for 30 min. Allow the solution to cool to room temperature, and dilute with *Buffer solution* to volume. Centrifuge a portion of the solution at high speed for 15 min, and pass a portion of the supernatant through a filter of 0.5-µm or finer pore size, discarding the first 4 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

**Flow rate:** 1 mL/min

**Injection volume:** 80 µL

**Run time:** NLT 7 times the retention time of felodipine

**System suitability**

**Samples:** *Standard solution and Sensitivity solution*

[Note—See *Table 4* for relative retention times.]

**Suitability requirements**

**Resolution:** NLT 1.5 between felodipine related compound A and felodipine, *Standard solution*

**Relative standard deviation:** NMT 5.0% for both felodipine and felodipine related compound A peaks, *Standard solution*

**Signal-to-noise ratio:** NLT 10 for the felodipine peak, *Sensitivity solution*

**Analysis**

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

Calculate the percentage of felodipine 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 felodipine related compound A from the *Sample solution*

$r_S$ = peak response of felodipine related compound A from the *Standard solution*

$C_S$ = concentration of USP Felodipine Related Compound A RS in the *Standard solution* (mg/mL)

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

Calculate the percentage of any unspecified impurity in the portion of Tablets taken:

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

$r_U$ = peak response of each unspecified impurity from the *Sample solution*

$r_S$ = peak response of felodipine from the *Standard solution*

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

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

**Acceptance criteria:** See *Table 4*. The reporting threshold is 0.05%.

**Table 4**

| Name | Relative Retention Time | Acceptance Criteria, NMT (%) |
|---|---|---|
| ▲Dimethyl felodipine▲ (USP 1-Aug-2022) [a,b] | 0.7 | — |
| Felodipine related compound A | 0.8 | 2.0 |
| Felodipine | 1.0 | — |
| ▲Diethyl felodipine▲ (USP 1-Aug-2022) [b,c] | 1.4 | — |
| Any unspecified impurity | — | 0.2 |
| Total impurities | — | 3.0 |

[a] Dimethyl 4-(2,3-dichlorophenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate.

[b] Process impurity included in the table for identification only. Process impurities are controlled in the drug substance and are not to be reported or included in the total impurities for the drug product.

[c] Diethyl 4-(2,3-dichlorophenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate.

## ADDITIONAL REQUIREMENTS

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

USP Felodipine RS

USP Felodipine Related Compound A RS

3-Ethyl 5-methyl 4-(2,3-dichlorophenyl)-2,6-dimethylpyridine-3,5-dicarboxylate.

$C_{18}H_{17}Cl_2NO_4$ 382.24

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

| Topic/Question | Contact | Expert Committee |
|---|---|---|
| FELODIPINE EXTENDED-RELEASE TABLETS | Documentary Standards Support | SM22020 Small Molecules 2 |

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