

Felodipine Extended-Release Tablets

» Felodipine Extended-Release Tablets contain not less than 90.0 percent and not more than 110.0 percent of the labeled amount of felodipine ($C_{18}H_{19}Cl_2NO_4$).

Packaging and storage—Preserve in tight containers.

USP Reference standards <11>—USP Felodipine RS. USP Felodipine Related Compound A RS.

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.

Identification—The retention time of the major peak in the chromatogram of the *Assay preparation* corresponds to that in the chromatogram of the *Standard preparation*, as obtained in the *Assay*.

Change to read:

Dissolution <711>—

TEST 1—

Medium: pH 6.5 phosphate buffer with 1% sodium lauryl sulfate; 500 mL. (*Medium* is prepared as follows. Transfer 206 mL of 1 M monobasic sodium phosphate monohydrate, 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 approximately 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, and mix well.)

Apparatus 2: 50 rpm.

Times: 2, 6, and 10 hours.

Buffer solution—Prepare as directed in the *Assay*.

Mobile phase—Prepare a filtered and degassed mixture of acetonitrile, *Buffer solution*, and methanol (2.5 : 2 : 1). Make adjustments if necessary (see *System Suitability* under *Chromatography* <621>).

Standard stock solution—Dissolve an accurately weighed quantity of USP Felodipine RS in alcohol to obtain a solution having a known concentration of 0.25 mg per mL.

Standard solution—Dilute an accurately measured volume of the *Standard stock solution* quantitatively, and stepwise if necessary, with *Medium* to obtain a solution having a known concentration of USP Felodipine RS equivalent to the concentration that would result from about 60% dissolution of a single Tablet in 500 mL of *Medium*.

Test solution—Place each Tablet in a specially made quadrangular basket of stainless steel wire gauze, soldered in one of its upper, narrow sides to the end of a steel rod (see *Figure 1*). Place the Tablet cover in the horizontal diagonal of the basket. Put the rod assembly up through the cover of the dissolution vessel, and fix it by means of two teflon nuts, 3.2 cm from the center of the vessel, or by any other appropriate means. Adjust the lower edge of the bottom of the basket to approximately 1 cm above the top of the paddle blade (see *Figure 2*). Orient the large side of the basket tangentially to the flow stream with the Tablet standing on its edge. Pass a 10-mL portion of the solution under test, obtained at each time interval, through a suitable filter.

Chromatographic system—Proceed as directed in the *Assay*.

Procedure—Separately inject equal volumes (100 μ L) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the areas for the major peaks.

Calculate the quantity, in mg, of felodipine ($C_{18}H_{19}Cl_2NO_4$) dissolved in the *Medium* by the formula:

$$CD(r_U / r_S)$$

in which *C* is the concentration, in mg per mL, of USP Felodipine RS in the *Standard solution*; *D* is the dilution factor used in preparing the *Test solution*; and r_U and r_S are the felodipine peak areas obtained from the *Test solution* and the *Standard solution*, respectively.

Tolerances—The percentages of the labeled amount of $C_{18}H_{19}Cl_2NO_4$ dissolved at the times specified conform to *Acceptance Table 2*.

Time (hours)	Amount dissolved
2	between 10% and 30%
6	between 42% and 68%
10	not less than 75%

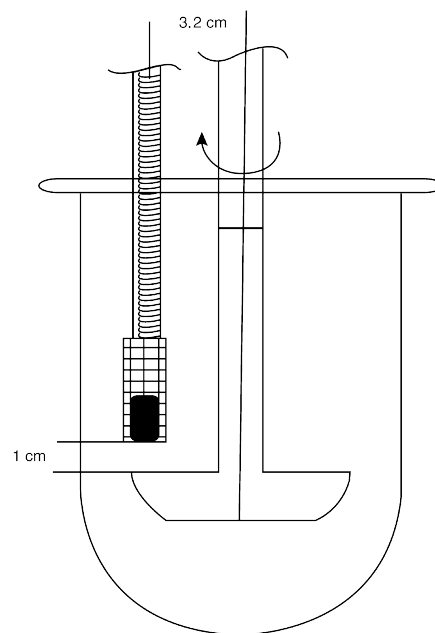


Figure 2. Drug Release Stationary Tablet Basket Configuration Diagram

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

Medium: 1% (w/v) polysorbate 80 in water; 500 mL.

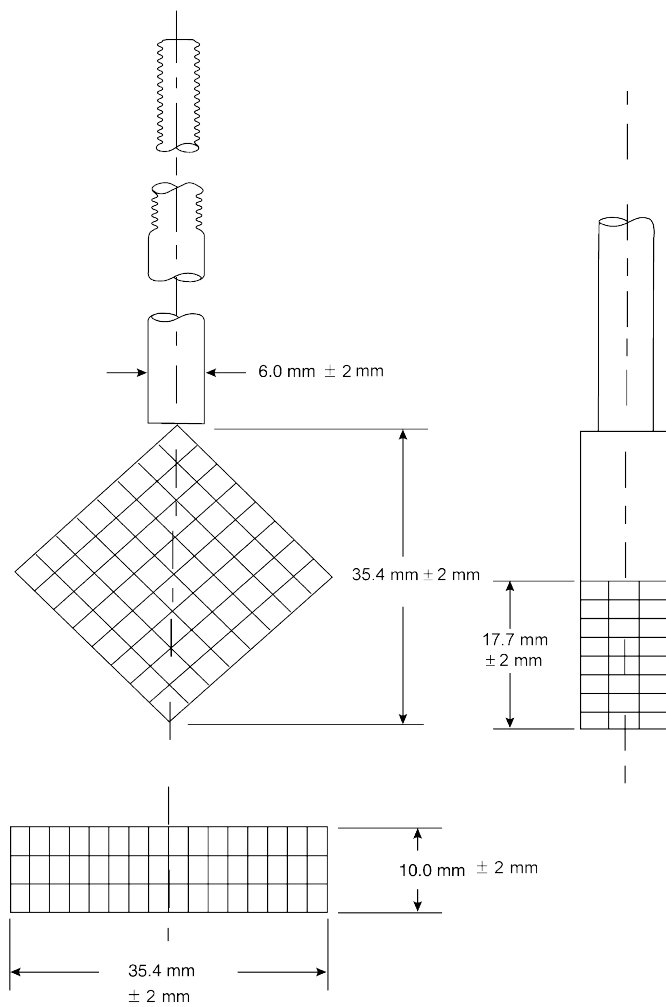
Apparatus 1: 100 rpm.

Times: 1, 4, and 8 hours.

Determine the amount of $C_{18}H_{19}Cl_2NO_4$ dissolved by employing the following method.

Buffer solution—Transfer 6.9 g, accurately weighed, of monobasic sodium phosphate into a 1-L volumetric flask containing about 400 mL of water. Add 8.0 mL of 1 M phosphoric acid, dilute with water to volume, and mix.

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NOTES

1. Rod and Basket with a Tablet cover placed in the horizontal diagonal of the basket.
2. Basket and Tablet cover material; stainless steel.
3. Basket gauze wire size: 8 mesh.

Figure 1. Stationary Tablet Basket

Mobile phase—Prepare a filtered and degassed mixture of *Buffer solution*, acetonitrile, and methanol (2 : 2 : 1). Make adjustments if necessary (see *System Suitability* under *Chromatography* (621)).

Standard stock solution—Transfer 40 mg, accurately weighed, of USP Felodipine RS into a 200-mL volumetric flask, and add about 200 mL of methanol. Sonicate for 2 minutes, cool, dilute with methanol to volume, and mix.

Standard working solutions—Transfer the appropriate volume of *Standard stock solution* into a suitable volumetric flask according to the following table.

Tablet Label Claim (mg)	Volume Transferred (mL)	Volumetric Flask (mL)
10	10	100
5	5	100
2.5	2.5	100

Dilute with *Medium* to volume, and mix.

Test solution—Pass a portion of the solution under test through a suitable 0.45-μm filter. Replace the withdrawn amount with *Medium*.

Chromatographic system (see *Chromatography* (621))—The liquid chromatograph is equipped with a 254-nm detector and a 4.6-mm × 15-cm column that contains packing L1. The flow rate is about 1 mL per minute. Chromatograph the *Standard working solution*, and record the peak responses as directed for *Procedure*: the capacity factor (*k'*) is not less than 5; the column efficiency (*N*) is not less than 1500 theoretical plates; the tailing factor is not more than 1.5; and the relative standard deviation for replicate injections is not more than 2.0%.

Procedure—Separately inject equal volumes (about 20 μL) of the *Standard working solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the peak responses. Calculate the quantity, in mg, of felodipine (C₁₈H₁₉Cl₂NO₄) dissolved by the formula:

$$C_U = \frac{r_U \times C_S}{r_S}$$

in which C_U is the concentration, in mg per mL, of felodipine in the sample at each time point; r_U and r_S are the peak responses obtained from the *Test solution* and the *Standard working solution*, respectively; and C_S is the concentration, in mg per mL, of felodipine in the *Standard working solution*.

Calculate the amount, in percentage, of felodipine ($C_{18}H_{19}Cl_2NO_4$) dissolved, with volume correction, by the formula:

$$\frac{\left\{ C_N \times [500 - V_U(n - 1)] \right\} + \left[\sum_{i=1}^{n-1} C_i \times V_U \right]}{LC} \times 100$$

in which C_N is the concentration, in mg per mL, of felodipine in the *Test solution* at each time point; 500 is the volume, in mL, of *Medium*; V_U is the volume, in mL, of sample withdrawn at each time point; n is the time point (at 4 hours, $n + 1$), summation of the concentration of the *Test solution* from the first to the $(n - 1)^{th}$ time point (only applicable for $n = 2$); 100 is the conversion factor to percentage; and LC is the Tablet label claim, in mg.

Tolerances—The percentages of the labeled amount of felodipine dissolved at the times specified conform to *Acceptance Table 1*.

Time (hours)	Amount dissolved
1	between 5% and 30%
4	between 45% and 70%
8	not less than 80%

• **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 by dissolving 5.7 g of monobasic sodium phosphate monohydrate and 2.8 g of dibasic sodium phosphate in 1000 mL of water, adding 10 g of sodium lauryl sulfate, and mixing. Adjust, if necessary, with diluted sodium hydroxide to a pH of 6.5 ± 0.05); 500 mL.

Apparatus 2: 50 rpm.

Times: 2, 6, and 10 hours.

Buffer solution—Dissolve 6.9 g of monobasic sodium phosphate monohydrate in 1000 mL of water. Adjust with phosphoric acid to a pH of 3.0 ± 0.05 .

Mobile phase—Prepare a filtered and degassed mixture of *Buffer solution*, acetonitrile and methanol (30 : 45 : 25). Make adjustments if necessary (see *System suitability* under *Chromatography* (621)).

Standard stock solution—Transfer 25 mg, accurately weighed, of USP Felodipine RS into a 50-mL volumetric flask, and dissolve in methanol with sonication. Allow the solution to cool to room temperature, and dilute with methanol to volume.

Working standard solution—Transfer 2.0 mL of the *Standard stock solution* to a 100-mL volumetric flask, and dilute with *Medium* to volume. This solution is stable for 5 days at room temperature.

Test solution—Place each Tablet in a specially made quadrangular basket of stainless steel wire gauze, soldered in one of its upper, narrow sides to the end of a steel rod (see *Figure 1* under *Test 1*). Place the Tablet cover in the horizontal diagonal of the basket. Put the rod assembly up through the cover of the dissolution vessel, and fix it by means of two teflon nuts 3.2 cm from the center of the vessel, or by any other appropriate means. Adjust the lower edge of the bottom of the basket to approximately 1 cm above the top of the paddle blade (see *Figure 2* under *Test 1*). Orient the large side of the basket tangentially to the flow stream with the Tablet standing on its edge. Pass a 10-mL portion of the solution under test, obtained at each time interval, through a suitable filter, discarding the first few mL.

Chromatographic system (see *Chromatography* (621))—The liquid chromatograph is equipped with a 362-nm detector and a 4.6-mm \times 15-cm column that contains 5- μ m packing L1. The flow rate is about 2.0 mL per minute. Chromatograph the *Working standard solution*, and record the peak responses as directed for *Procedure*: the column efficiency is not less than 1500 theoretical plates; and the relative standard deviation is not more than 2.0%.

Procedure—Separately inject equal volumes (about 40 μ L) of the *Working standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the peak responses. Calculate the percentage of felodipine dissolved by the formula:

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

in which r_U and r_S are the peak responses for the *Test solution* and the *Working standard solution*, respectively, C_S is the concentration, in mg per mL, of the *Working standard solution*, L is the Tablet label claim in mg, V is the volume (mL) of *Medium*, and 100 is the conversion factor to percentage.

Tolerances—The percentages of the labeled amount of felodipine dissolved at the times specified conform to *Acceptance Table 1*.

Time (hours)	Amount dissolved
2	between 10% and 30%
6	between 50% and 80%
10	not less than 80%

• (RB 2-Nov-2009)

Uniformity of dosage units (905): meet the requirements.

PROCEDURE FOR CONTENT UNIFORMITY—

Buffer solution, **Mobile phase**, **Standard stock preparation**, and **Chromatographic system**—Proceed as directed in the *Assay*.

Standard solution—Use the *Standard preparation*, prepared as directed in the *Assay*.

Test solution—Transfer 1 Tablet to a 100-mL volumetric flask, add 40 mL of acetonitrile, and sonicate for 20 minutes with occasional swirling. Add 20 mL of methanol, and shake by mechanical means for 30 minutes. Allow to cool to room temperature, dilute with *Buffer solution* to volume, and mix. Centrifuge a portion of the solution at high speed for 15 minutes. Dilute a portion of the supernatant with *Mobile phase* to obtain a solution containing about 20 μ g of felodipine per mL. Pass this solution through a filter having a 0.5- μ m or finer porosity.

Procedure—Separately inject equal volumes (about 40 μ L) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in mg, of felodipine ($C_{18}H_{19}Cl_2NO_4$) in the Tablet taken by the formula:

$$(TC/D)(r_U / r_S)$$

in which T is the labeled quantity, in mg, of felodipine in the Tablet; C is the concentration, in μ g per mL, of USP Felodipine RS in the *Standard solution*; D is the concentration, in μ g per mL, of felodipine in the *Test solution*, based on the labeled quantity per Tablet and the extent of dilution; and r_U and r_S are the felodipine peak responses obtained from the *Test solution* and the *Standard solution*, respectively.

Related compounds—

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

Standard stock solution 1—Dissolve an accurately weighed quantity of USP Felodipine Related Compound A RS in methanol to obtain a solution having a known concentration of about 0.2 mg per mL. Transfer 10.0 mL of this solution to a 100-mL volumetric flask, dilute with *Mobile phase* to volume, and mix.

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Standard stock solution 2—Dissolve an accurately weighed quantity of USP Felodipine RS in methanol, and dilute quantitatively, and stepwise if necessary, with methanol to obtain a solution having a known concentration of about 2 mg per mL.

System suitability solution—Transfer 15.0 mL of *Standard stock solution 1* and 5.0 mL of *Standard stock solution 2* to a 100-mL volumetric flask, dilute with *Mobile phase* to volume, and mix.

Standard solution—Transfer 10.0 mL of *Standard stock solution 1* to a 100-mL volumetric flask, dilute with *Mobile phase* to volume, and mix.

Test solution—Proceed as directed for the *Assay preparation* in the *Assay*, except that after centrifuging a portion of the solution at high speed for 15 minutes, pass a portion of the supernatant through a filter having a 0.5- μ m or finer porosity, discarding the first 4 mL of the filtrate.

Chromatographic system (see *Chromatography* <621>)—The liquid chromatograph is equipped with a 254-nm detector and a 4.6-mm \times 15-cm column that contains packing L1. The flow rate is about 1 mL per minute. Chromatograph the *System suitability solution*, and record the peak responses as directed for *Procedure*: the relative retention times are 0.75 for felodipine related compound A and 1.0 for felodipine; the resolution, *R*, between felodipine and felodipine related compound A is not less than 1.5; and the column efficiency is not less than 1500 theoretical plates.

Procedure—Separately inject equal volumes (about 40 μ L) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the peak responses for felodipine related compound A. Calculate the percentage of felodipine related compound A in the portion of Tablets taken by the formula:

$$1000C(r_U/r_S)$$

in which *C* is the concentration, in mg per mL, of USP Felodipine Related Compound A RS in the *Standard solution*; and *r_U* and *r_S* are the peak responses of felodipine related compound A obtained from the *Test solution* and the *Standard solution*, respectively: not more than 2.0% is found.

Assay—

Buffer solution—Dissolve 6.9 g of monobasic sodium phosphate in about 800 mL of water in a 1000-mL volumetric flask. Adjust with 1 M phosphoric acid to a pH of 3.0 ± 0.05 , dilute with water to volume, and mix.

Mobile phase—Prepare a filtered and degassed mixture of *Buffer solution*, acetonitrile, and methanol (2 : 2 : 1). Make adjustments if necessary (see *System Suitability* under *Chromatography* <621>).

Standard stock preparation—Dissolve an accurately weighed quantity of USP Felodipine RS in methanol, and dilute quantitatively, and stepwise if necessary, with methanol to obtain a solution having a known concentration of about 2 mg per mL.

Standard preparation—Dilute an accurately measured volume of the *Standard stock preparation* quantitatively and stepwise with *Mobile phase* to obtain a solution having a known concentration of about 0.02 mg per mL.

Assay preparation—Weigh and finely powder not fewer than 10 Tablets. Transfer an accurately weighed portion of the powder, equivalent to about 10 mg of felodipine, to a 100-mL volumetric flask, add 40 mL of acetonitrile and 20 mL of methanol, and sonicate for 5 minutes. Add about 30 mL of *Buffer solution*, and shake by mechanical means for 30 minutes. Allow the solution to cool to room temperature, dilute with *Buffer solution* to volume, and mix. Centrifuge a portion of the solution at high speed for 15 minutes. Transfer 10 mL of the supernatant to a 50-mL volumetric flask, dilute with *Mobile phase* to volume, and mix. Pass a portion of this solution through a filter having a 0.5- μ m or finer porosity, discarding the first 4 mL of the filtrate.

Chromatographic system (see *Chromatography* <621>)—The liquid chromatograph is equipped with a 362-nm detector and a 4.6-mm \times 15-cm column that contains packing L1. The flow rate is about 1 mL per minute. Chromatograph the *Standard preparation*, and record the peak responses as directed for *Procedure*: the column efficiency is not less than 1500 theoretical plates; and the relative standard deviation for replicate injections is not more than 2.0%.

Procedure—Separately inject equal volumes (about 40 μ L) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in mg, of felodipine ($C_{18}H_{19}Cl_2NO_4$) in the portion of Tablets taken by the formula:

$$500C(r_U/r_S)$$

in which *C* is the concentration, in mg per mL, of USP Felodipine RS in the *Standard preparation*; and *r_U* and *r_S* are the peak responses obtained from the *Assay preparation* and the *Standard preparation*, respectively.