Fenofibrate Capsules

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Reason for Revision	Compliance

In accordance with the Rules and Procedures of the 2015-2020 Council of Experts, the Chemical Medicines Monographs 2 Expert Committee has revised the Fenofibrate Capsules. The purpose for the revision is to add *Dissolution Test 5* to accommodate the FDA approved Fenofibrate Capsules drug products with different dissolution conditions and tolerance than the existing dissolution test.

The Fenofibrate Capsules Revision Bulletin supersedes the currently official Fenofibrate Capsules monograph. The Revision Bulletin will be incorporated in the *Second Supplement* to *USP 41–NF 36*.

Should you have any questions, please contact Sujatha Ramakrishna, Principal Scientific Liaison (301-816-8349 or sxr@usp.org) and Yanyin Yang, Associate Scientific Liaison (301-692-3623 or Yanyin.Yang@usp.org)

Fenofibrate Capsules

DEFINITION

Fenofibrate Capsules contain NLT 90.0% and NMT 110.0% of the labeled amount of fenofibrate ($C_{20}H_{21}ClO_4$).

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*.

ASSAY

• **PROCEDURE**

Use *Sample stock solution 2* for Capsules labeled to meet the requirements of *Dissolution Test 2.* For all other products, use *Sample stock solution 1.*

Solution A: 136 mg/L of monobasic potassium phosphate in water. Adjust with dilute phosphoric acid (1 in 10) to a pH of 2.9 ± 0.05.

Mobile phase: Methanol and *Solution A* (4:1)

Standard solution: 67 µg/mL of USP Fenofibrate RS in *Mobile phase*

Sample stock solution 1: Accurately weigh the contents of NLT 20 Capsules. Mix the contents, and transfer a weighed portion of the powder, equivalent to about 67 mg of fenofibrate, to a 100-mL volumetric flask. Add 80 mL of *Mobile phase*, sonicate for 10 min, stir for 15 min, and dilute with *Mobile phase* to volume.

Sample stock solution 2 (for Capsules labeled to meet the requirements of *Dissolution Test 2*)**:** Weigh the contents of NLT 20 Capsules. Mix the contents, melt in an oven at 80° for NLT 30 min, and homogenize. Allow the sample to solidify. Transfer a weighed portion of the sample, equivalent to about 67 mg of fenofibrate, to a 100-mL volumetric flask, dissolve in 30 mL of methanol with the aid of a mechanical shaker for NLT 4 h, and dilute with *Mobile phase* to volume.

Sample solution: Nominally 67 µg/mL of fenofibrate from the designated *Sample stock solution*, in *Mobile phase*. Pass a portion of this solution through a polyvinylidene difluoride (PVDF) filter of 0.45-µm pore size, discarding the first 5 mL.

Chromatographic system
(See *Chromatography* ⟨621⟩*, System Suitability*.)
Mode: LC
Detector: UV 285 nm
Column: 4.6-mm × 15-cm; 5-µm packing L1
Flow rate: 1 mL/min
Injection volume: 20 µL

System suitability
Sample: *Standard solution*
Suitability requirements
Column efficiency: NLT 6000 theoretical plates
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 fenofibrate ($C_{20}H_{21}ClO_4$) in the portion of Capsules taken:

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

r_U = peak response from the *Sample solution*
r_S = peak response from the *Standard solution*
C_S = concentration of the *Standard solution* (µg/mL)
C_U = nominal concentration of the *Sample solution* (µg/mL)

Acceptance criteria: 90.0%–110.0%

PERFORMANCE TESTS

Change to read:

• **DISSOLUTION** ⟨711⟩

Test 1
Medium: 0.05 M sodium lauryl sulfate in water; 1000 mL, deaerated
Apparatus 2: 75 rpm
Time: 40 min
Solution A and **Mobile phase:** Proceed as directed in the *Assay*.
Standard solution: (0.001 × *L*) mg/mL of USP Fenofibrate RS in *Mobile phase*, where *L* is the label claim, in mg/Capsule
Sample solution: Pass a portion of the solution under test through a suitable PVDF filter of 0.45-µm pore size.
Chromatographic system
(See *Chromatography* ⟨621⟩*, System Suitability*.)
Mode: LC
Detector: UV 285 nm
Column: 4.6-mm × 15-cm; 5-µm packing L1
Flow rate: 1 mL/min
Injection volume: 10 µL for Capsules labeled to contain 67 mg; 5 µL for Capsules labeled to contain 134 or 200 mg
System suitability
Sample: *Standard solution*
Suitability requirements
Column efficiency: NLT 4000 theoretical plates
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 fenofibrate ($C_{20}H_{21}ClO_4$) dissolved:

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

r_U = peak response from the *Sample solution*
r_S = peak response from the *Standard solution*
C_S = concentration of the *Standard solution* (mg/mL)
L = label claim (mg/Capsule)
V = volume of *Medium*, 1000 mL
Tolerances: NLT 70% (*Q*) of the labeled amount of fenofibrate ($C_{20}H_{21}ClO_4$) is dissolved.

Test 2: If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 2*.
Medium: Phosphate buffer pH 6.8 ± 0.1 containing 0.1% pancreatin and 2% polysorbate 80; 900 mL, deaerated by vacuum
Apparatus 2: 75 rpm with sinkers (see *Dissolution* ⟨711⟩, *Figure 2a*)
Time: 2 h
Standard solution: (*L*/1000) mg/mL of USP Fenofibrate RS in *Medium*, where *L* is the Capsule label claim, in mg. A volume of methanol, not exceeding 10%, can be used in the first dilution to solubilize fenofibrate.
Sample solution: Pass 20 mL of the solution under test through a suitable PVDF filter of 0.45-µm pore size, discarding the first 2 mL.
Blank: *Medium*
Instrumental conditions
(See *Ultraviolet-Visible Spectroscopy* ⟨857⟩.)

Mode: Spectrophotometry
Detector: UV 288 nm
Path length: 0.1-cm flow cell
Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the percentage of the labeled amount of fenofibrate ($C_{20}H_{21}ClO_4$) dissolved:

$$\text{Result} = (A_U/A_S) \times (C_S/L) \times V \times 100$$

A_U = absorbance of the *Sample solution*
A_S = absorbance of the *Standard solution*
C_S = concentration of the *Standard solution* (mg/mL)
L = label claim (mg/Capsule)
V = volume of *Medium*, 900 mL

Tolerances: NLT 80% (Q) of the labeled amount of fenofibrate ($C_{20}H_{21}ClO_4$) is dissolved.

Test 3: If the product complies with this test, the labeling indicates that the product meets USP *Dissolution Test 3*.
Medium: 0.72% sodium lauryl sulfate in water; 1000 mL, deaerated
Apparatus 2: 75 rpm, with sinkers with three prongs
Time: 30 min
Standard solution: (L/10) mg/mL of USP Fenofibrate RS in methanol, where L is the Capsule label claim in mg. Transfer 10.0 mL of this solution to a 1000-mL volumetric flask, and dilute with *Medium* to volume.
Sample solution: Pass a portion of the solution under test through a suitable PVDF filter of 0.45-µm pore size. Dilute with *Medium*, if necessary.
Instrumental conditions
(See *Ultraviolet-Visible Spectroscopy* ⟨857⟩.)
Mode: Spectrophotometry
Detector: UV 290 nm
Blank: *Medium*
Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the percentage of the labeled amount of fenofibrate ($C_{20}H_{21}ClO_4$) dissolved:

$$\text{Result} = (A_U/A_S) \times (C_S/L) \times D \times V \times 100$$

A_U = absorbance of the *Sample solution*
A_S = absorbance of the *Standard solution*
C_S = concentration of the *Standard solution* (mg/mL)
L = label claim (mg/Capsule)
D = dilution for the *Sample solution*
V = volume of *Medium*, 1000 mL

Tolerances: NLT 80% (Q) of the labeled amount of fenofibrate ($C_{20}H_{21}ClO_4$) is dissolved.

Test 4: If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 4*.
Medium: 0.05 M sodium lauryl sulfate in water; 1000 mL
Apparatus 2: 75 rpm, with helix sinkers or hoseclamp sinkers
Times: 30 min for products labeled to contain 67 mg, 134 mg, and 200 mg; 40 min for products labeled to contain 43 mg and 130 mg
Standard stock solution: 0.5 mg/mL of USP Fenofibrate RS in *Medium* prepared as follows. Dissolve a suitable quantity of USP Fenofibrate RS, taken in a suitable volumetric flask, in about 6% of the total volume of methanol, and dilute with *Medium* to volume.
Standard solution: Prepare solutions of USP Fenofibrate RS in *Medium* as per *Table 1* from *Standard stock solution*

Table 1

Capsule Strength (mg)	Concentration (mg/mL)
67	0.065
130 and 134	0.13
200	0.2
43	0.045

Sample solution: Pass a portion of the solution under test through a suitable filter of 0.45-µm pore size, discarding the first 3 mL of the filtrate.
Instrumental conditions
(See *Ultraviolet-Visible Spectroscopy* ⟨857⟩.)
Mode: Spectrophotometry
Detector: UV 291 nm
Path length: 0.1-cm flow cell
Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the percentage of the labeled amount of fenofibrate ($C_{20}H_{21}ClO_4$) dissolved:

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

A_U = absorbance from the *Sample solution*
A_S = absorbance from the *Standard solution*
C_S = concentration of the *Standard solution* (mg/mL)
V = volume of *Medium*, 1000 mL
L = label claim (mg/Capsule)

Tolerances: NLT 80% (Q) of the labeled amount of fenofibrate ($C_{20}H_{21}ClO_4$) is dissolved.

•**Test 5:** If the product complies with this test, the labeling indicates that the product meets USP *Dissolution Test 5*.
Medium: 0.025 M sodium lauryl sulfate in water; 1000 mL, deaerated
Apparatus 2: 75 rpm, with suitable sinkers
Time: 20 min
Standard stock solution: 0.5 mg/mL of USP Fenofibrate RS in methanol. Sonicate if necessary.
Standard solution: 12.5 µg/mL of USP Fenofibrate RS prepared by diluting quantitatively from *Standard stock solution* with *Medium*
Sample solution: Pass a portion of the solution under test through a suitable filter of 0.45-µm pore size and discard the first few milliliters. Dilute quantitatively with *Medium* to the nominal concentration as per *Table 2*.

Table 2

Capsule Strength (mg)	Concentration (µg/mL)
30	12.0
90	13.5

Instrumental conditions
(See *Ultraviolet-Visible Spectroscopy* ⟨857⟩.)
Mode: Spectrophotometry
Detector: UV 290 nm
Blank: *Medium*
Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the percentage of the labeled amount of fenofibrate ($C_{20}H_{21}ClO_4$) dissolved:

$$\text{Result} = (A_U/A_S) \times (C_S/L) \times D \times V \times 100$$

A_U = absorbance of the *Sample solution*
A_S = absorbance of the *Standard solution*

C_S = concentration of the *Standard solution* (mg/mL)
L = label claim (mg/Capsule)
D = dilution for the *Sample solution*
V = volume of *Medium*, 1000 mL

Tolerances: NLT 80% (Q) of the labeled amount of fenofibrate ($C_{20}H_{21}ClO_4$) is dissolved.● (RB 1-Nov-2017)

• **UNIFORMITY OF DOSAGE UNITS** ⟨**905**⟩

Procedure for content uniformity

Solution A, Mobile phase, Standard solution, Chromatographic system, System suitability, and **Analysis:** Proceed as directed in the *Assay.*

Sample stock solution: Place 1 Capsule in a suitable volumetric flask, add *Solution A* to 10%–20% of the final volume, and stir for 20 min to disintegrate the Capsule. Fill the flask to about 80% with methanol, sonicate for 10 min, and stir for 15 min. Dilute with methanol to volume to obtain a solution having a known concentration of about 0.4–0.7 mg/mL of fenofibrate, based on the label claim.

Sample solution: 60–70 µg/mL of fenofibrate, from the *Sample stock solution*, in *Mobile phase*. Pass a portion of this solution through a PVDF filter of 0.45-µm pore size, discarding the first 5 mL.

Acceptance criteria: Meet the requirements

IMPURITIES

• **ORGANIC IMPURITIES**

Use *Sample solution 2* for Capsules labeled to meet the requirements of *Dissolution Test 2*. For all other products, use *Sample solution 1*.

Solution A: 136 mg/L of monobasic potassium phosphate. Adjust with dilute phosphoric acid (1 in 10) to a pH of 2.9 ± 0.05.

Mobile phase: Methanol and *Solution A* (4:1)

System suitability solution: 0.67 mg/mL of USP Fenofibrate RS and 3.35 µg/mL of USP Fenofibrate Related Compound B RS in *Mobile phase*

Standard solution: 3.35 µg/mL of USP Fenofibrate RS and 3.35 µg/mL of USP Fenofibrate Related Compound B RS in *Mobile phase*

Sensitivity solution: 0.67 µg/mL of USP Fenofibrate RS and 0.67 µg/mL of USP Fenofibrate Related Compound B RS in *Mobile phase*, from the *Standard solution*

Sample solution 1: Accurately weigh the contents of NLT 20 Capsules. Mix the contents, and transfer a weighed portion of the powder, equivalent to about 67 mg of fenofibrate, to a 100-mL volumetric flask. Add 80 mL of *Mobile phase*, sonicate for 10 min, stir for 15 min, and dilute with *Mobile phase* to volume. Pass a portion of this solution through a PVDF filter of 0.45-µm pore size, discarding the first 5 mL. The final concentration based on the label claim is about 0.67 mg/mL.

Sample solution 2 (for Capsules labeled to meet the requirements of *Dissolution Test 2*)**:** Weigh the contents of NLT 20 Capsules. Mix the contents, melt in an oven at 80° for NLT 30 min, and homogenize. Allow the sample to solidify. Transfer a weighed portion of the sample, equivalent to about 67 mg of fenofibrate, to a 100-mL volumetric flask, dissolve in 30 mL of methanol with the aid of a mechanical shaker for NLT 4 h, and dilute with *Mobile phase* to volume. Pass through a PVDF filter of 0.45-µm pore size, discarding the first 1–2 mL. The final concentration based on the label claim is about 0.67 mg/mL.

Chromatographic system

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

Mode: LC
Detector: UV 285 nm
Column: 4.6-mm × 15-cm; 5-µm packing L1
Flow rate: 1 mL/min
Injection volume: 20 µL

System suitability

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

Suitability requirements

Resolution: NLT 3.0 between fenofibrate and fenofibrate related compound B, *System suitability solution*

Column efficiency: NLT 3000 theoretical plates for fenofibrate related compound B, *System suitability solution*

Tailing factor: NMT 2.0 for fenofibrate related compound B, *System suitability solution*

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

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

Analysis

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

Calculate the percentage of fenofibrate related compound B in the portion of Capsules taken:

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

r_U = peak response of fenofibrate related compound B from the *Sample solution*
r_S = peak response of fenofibrate related compound B from the *Standard solution*
C_S = concentration of fenofibrate related compound B in the *Standard solution* (mg/mL)
C_U = nominal concentration of fenofibrate in the *Sample solution* (mg/mL)

Calculate the percentage of any other impurity in the portion of Capsules taken:

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

r_U = peak response of each individual impurity from the *Sample solution*
r_S = peak response of fenofibrate from the *Standard solution*
C_S = concentration of fenofibrate in the *Standard solution* (mg/mL)
C_U = nominal concentration of fenofibrate in the *Sample solution* (mg/mL)

Acceptance criteria

Individual impurities: NMT 0.5% for fenofibrate related compound B; NMT 0.2% for any other individual impurity

Total impurities: NMT 2.0%

ADDITIONAL REQUIREMENTS

• **PACKAGING AND STORAGE:** Preserve in well-closed containers, and 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 Fenofibrate RS
USP Fenofibrate Related Compound B RS
2-[4-(4-Chlorobenzoyl)phenoxy]-2-methylpropanoic acid, or fenofibric acid.