Fenofibrate Capsules

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Expert Committee: Chemical Medicines Monographs 2
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 (C20H21ClO4).

**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 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 (C20H21ClO4) dissolved:

\[ \text{Result} = \left( \frac{r_U}{r_s} \times \frac{C_s}{C_t} \right) \times 100 \]

- \( r_U \) = peak response from the Sample solution
- \( r_s \) = peak response from the Standard solution
- \( C_s \) = concentration of the Standard solution (µg/mL)
- \( C_t \) = nominal concentration of the Sample solution (µg/mL)

**Acceptance criteria**: 90.0%–110.0%

**PERFORMANCE TESTS**

**Change to read:**

- **DISTRIBUTION (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 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 (C20H21ClO4) dissolved:

  \[ \text{Result} = \left( \frac{r_U}{r_s} \times \frac{C_s}{C_t} \right) \times 100 \]

  where

  - \( r_U \) = 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
  - \( Q \) = volume of USP Fe-nofibrate (C20H21ClO4) 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).)
Fenofibrate

**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 (C20H21ClO4) dissolved:

\[
\text{Result} = \frac{A_U}{A_S} \times \left( \frac{C_S}{L} \right) \times V \times 100
\]

- \(A_U\) = 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 (C20H21ClO4) 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 suitable sinkers

- **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 (C20H21ClO4) dissolved:

\[
\text{Result} = \frac{A_U}{A_S} \times \left( \frac{C_S}{L} \right) \times V \times 100
\]

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

**Tolerances:** NLT 80% (Q) of the labeled amount of fenofibrate (C20H21ClO4) 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

- **Time:** 20 min

**Standard solution:** 0.5 mg/mL of USP Fenofibrate RS in methanol. Sonicate if necessary.

**Standard stock 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 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 (C20H21ClO4) dissolved:

\[
\text{Result} = \frac{A_U}{A_S} \times \left( \frac{C_S}{L} \right) \times V \times 100
\]

- \(A_U\) = absorbance of the Sample solution
- \(A_S\) = absorbance of the Standard solution

### Table 1

<table>
<thead>
<tr>
<th>Capsule Strength (mg)</th>
<th>Concentration (mg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>67</td>
<td>0.065</td>
</tr>
<tr>
<td>130 and 134</td>
<td>0.13</td>
</tr>
<tr>
<td>200</td>
<td>0.2</td>
</tr>
<tr>
<td>43</td>
<td>0.045</td>
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</tbody>
</table>

### Table 2

<table>
<thead>
<tr>
<th>Capsule Strength (mg)</th>
<th>Concentration (µg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>30</td>
<td>12.0</td>
</tr>
<tr>
<td>90</td>
<td>13.5</td>
</tr>
</tbody>
</table>

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ORGANIC IMPURITIES

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

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°C 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:

\[
\text{Result} = \left( \frac{r_U}{R_U} \right) \times \left( \frac{C_S}{C_U} \right) \times 100
\]

where:
- \( r_U \) = peak response of fenofibrate related compound B from the Sample solution
- \( R_U \) = 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:

\[
\text{Result} = \left( \frac{r_i}{R_i} \right) \times \left( \frac{C_S}{C_U} \right) \times 100
\]

where:
- \( r_i \) = peak response of each individual impurity from the Sample solution
- \( R_i \) = peak response of fenofibrate from the Standard solution
- \( C_i \) = 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 fenofibr acid.