**Alprazolam Orally Disintegrating Tablets**

**DEFINITION**
Alprazolam Orally Disintegrating Tablets contain NLT 90.0% and NMT 110.0% of the labeled amount of alprazolam (C₁₇H₁₃ClN₄).

**IDENTIFICATION**
- 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**
  - **Buffer:** 6.8 g/L of monobasic potassium phosphate in water. Adjust with phosphoric acid or potassium hydroxide to a pH of 3.5.
  - **Diluent:** Acetonitrile and water (60:40)
  - **Mobile phase:** Acetonitrile, methanol, and Buffer (35:10:55)
  - **Standard solution:** 10 μg/mL of USP Alprazolam RS in Dilluent
  - **Sample solution:** 10 μg/mL of alprazolam in Dilluent. Prepare using 10 Tablets, and pass through a suitable filter. [NOTE—Sonicate with intermittent shaking to help dissolve, if necessary.]

**Chromatographic system**
(See Chromatography (621), System Suitability.)
- **Mode:** LC
- **Detector:** UV 221 nm
- **Column:** 4.6-mm × 15-cm; 5-μm packing L7
- **Column temperature:** 30°
- **Flow rate:** 1.5 mL/min
- **Injection volume:** 30 μL

**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
- **Calculation:** The percentage of the labeled amount of alprazolam (C₁₇H₁₃ClN₄) in the portion of Tablets taken:

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

  \[
  r_U = \text{peak response from the Sample solution}
  \]

  \[
  r_S = \text{peak response from the Standard solution}
  \]

  \[
  C_S = \text{concentration of USP Alprazolam RS in the Standard solution (μg/mL)}
  \]

  \[
  C_U = \text{nominal concentration of alprazolam in the Sample solution (μg/mL)}
  \]

**Acceptance criteria:** 90.0%–110.0%

**PERFORMANCE TESTS**

**Dissolution (711)**
- **Test 1** (88 1-May-2012)
  - **Medium:** pH 6.0 phosphate buffer (8 g/L of monobasic potassium phosphate and 2 g/L of dibasic potassium phosphate in water. Adjust with phosphoric acid or potassium hydroxide to a pH of 6.0 ± 0.1) (88 1-May-2012)
  - **Apparatus 2:** 50 rpm
  - **Time:** 10 min
  - **Mobile phase:** Acetonitrile and Buffer (35:65)
  - **Standard stock solution:** 50 μg/mL of USP Alprazolam RS in methanol. [NOTE—Sonicate to help dissolve, if necessary.]
  - **Standard solution:** (L/1000) μg/mL of USP Alprazolam RS in Medium from the Standard stock solution, where L is the label claim in μg/Tablet
  - **Sample solution:** Pass a portion of the solution under test through a suitable filter of 0.45-μm pore size, discarding the first few mL.

**Analysis**
- **Samples:** Standard solution and Sample solution
- **Calculation:** The percentage of the labeled amount of alprazolam (C₁₇H₁₃ClN₄) dissolved:

  \[
  \text{Result} = \left( \frac{r_U}{r_S} \right) \times C_S \times V \times \left( \frac{1}{l/L} \right) \times 100
  \]

  \[
  r_U = \text{peak response from the Sample solution}
  \]

  \[
  r_S = \text{peak response from the Standard solution}
  \]

  \[
  C_S = \text{concentration of USP Alprazolam RS in the Standard solution (μg/mL)}
  \]

  \[
  V = \text{volume of Medium, 900 mL}
  \]

  \[
  L = \text{label claim (mg/Tablet)}
  \]

  **Tolerances:** NLT 80% (Q) of the labeled amount of alprazolam (C₁₇H₁₃ClN₄) is dissolved.

- **Test 2:** If the product complies with this test, the labeling indicates that it meets USP Dissolution Test 2.
  - **Medium:** pH 6.0 phosphate buffer (8 g/L of monobasic potassium phosphate and 2 g/L of dibasic potassium phosphate in water. Adjust with phosphoric acid or potassium hydroxide to a pH of 6.0 ± 0.1); 500 mL
  - **Apparatus 2:** 50 rpm
  - **Time:** 10 min
  - **Buffer:** 1.36 g/L of monobasic potassium phosphate adjusted with dilute sodium hydroxide to a pH of 6.0
  - **Mobile phase:** Acetonitrile and Buffer (35:65)
  - **Standard stock solution:** 50 μg/mL of USP Alprazolam RS in methanol. [NOTE—Sonicate to help dissolve, if necessary.]
  - **Standard solution:** (L/500) μg/mL of USP Alprazolam RS in Medium from the Standard stock solution, where L is the label claim in μg/Tablet
  - **Sample solution:** Pass a 5-mL aliquot of the solution under test through a suitable filter of 0.45-μm pore size, discarding the first 3 mL.

**Chromatographic system**
(See Chromatography (621), System Suitability.)
- **Mode:** LC
- **Detector:** UV 230 nm
- **Column:** 4.6-mm × 7.5-cm; 5-μm packing L7
- **Flow rate:** 1.5 mL/min
- **Injection volume:** 40 μL
- **Run time:** 3 times the retention time of alprazolam
Alprazolam

**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 alprazolam (C₁₇H₁₃ClN₄) dissolved:

\[
\text{Result} = \left( \frac{r_U}{r_S} \right) \times \left( \frac{C_i}{C_0} \right) \times \left( \frac{V}{L} \right) \times 100
\]

- \( r_U \) = peak response from the **Sample solution**
- \( r_S \) = peak response from the **Standard solution**
- \( C_i \) = concentration of USP Alprazolam RS in the **Standard solution** (µg/mL)
- \( C_0 \) = nominal concentration of alprazolam in the **Sample solution** (µg/mL)
- \( F \) = relative response factor (see Table 2)

Acceptance criteria: See Table 2. Disregard any peaks less than 0.05%.

**Tolerances:** NLT 70% \( (Q) \) of the labeled amount of alprazolam \( (C₁₇H₁₃ClN₄) \) is dissolved.

**Uniformity of Dosage Units** (905):
- Meet the requirements

**Impurities**

- **Organic Impurities**
  - Buffer and Diluent: Prepare as directed in the Assay.
  - Solution A: Acetonitrile, methanol, and Buffer (25:20:55)
  - Solution B: Acetonitrile, methanol, and Buffer (40:5:55)
  - Mobile phase: See Table 1.

**Table 1**

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>Solution A (%)</th>
<th>Solution B (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>100</td>
<td>0</td>
</tr>
<tr>
<td>12</td>
<td>100</td>
<td>0</td>
</tr>
<tr>
<td>15</td>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td>60</td>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td>65</td>
<td>100</td>
<td>0</td>
</tr>
<tr>
<td>70</td>
<td>100</td>
<td>0</td>
</tr>
</tbody>
</table>

**Standard solution:** 0.6 µg/mL of USP Alprazolam RS in **Diluent**

**Sample solution:** 200 µg/mL of alprazolam in **Diluent**. Prepare using 10 Tablets, and pass through a suitable filter.

**Chromatographic system**

(See Chromatography 〈621〉, System Suitability.)

- Mode: LC
- Detector: UV 240 nm
- Column: 4.6-mm × 15-cm; 5-µm packing L7
- Column temperature: 30°
- Flow rate: 1.2 mL/min
- Injection volume: 25 µL

**System suitability**

Sample: **Standard solution**

Suitability requirements:
- Theoretical plates: NLT 2000
- Tailing factor: NMT 1.5
- Relative standard deviation: NMT 6.0%

**Analysis**

Samples: **Standard solution and Sample solution**

Calculate the percentage of each impurity in the portion of Tablets taken:

\[
\text{Result} = \left( \frac{r_U}{r_S} \right) \times \left( \frac{C_i}{C_0} \right) \times \left( \frac{V}{L} \right) \times 100
\]

- \( r_U \) = peak response of each impurity from the **Sample solution**
- \( r_S \) = peak response of alprazolam from the **Standard solution**
- \( C_i \) = concentration of USP Alprazolam RS in the **Standard solution** (µg/mL)
- \( C_0 \) = nominal concentration of alprazolam in the **Sample solution** (µg/mL)
- \( F \) = relative response factor (see Table 2)

**Table 2**

<table>
<thead>
<tr>
<th>Name</th>
<th>Relative Retention Time</th>
<th>Relative Response Factor</th>
<th>Acceptance Criteria, NMT (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alprazolam related compound A(^{a,b} )</td>
<td>0.8</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Alprazolam</td>
<td>1.0</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>2-Amino-5-chlorobenzophenone</td>
<td>2.9</td>
<td>1.9</td>
<td>0.5</td>
</tr>
<tr>
<td>Any other unknown impurity</td>
<td>—</td>
<td>1.0</td>
<td>0.5</td>
</tr>
<tr>
<td>Total impurities</td>
<td>—</td>
<td>—</td>
<td>2.0</td>
</tr>
</tbody>
</table>

\(^{a}2\text{-}(2\text{-Acetylhydrazino})-7\text{-chloro}-5\text{-phenyl}-3\text{H}-1,4\text{-benzodiazepine.}\)

\(^{b}\text{Disregard the peak due to alprazolam related compound A, because it is a process impurity in alprazolam.}\)

**Addition Requirements**

- **Packaging and Storage:** Preserve in tight containers, and store at controlled room temperature.

Add the following:

**Labeling:** When more than one Disintegration test is given, the labeling states the Disintegration test used only if Test 1 is not used. When more than one Dissolution test is given, the labeling states the Dissolution test used only if Test 1 is not used.\(^{(RB 1\text{-May-2012)}}\)

**USP Reference Standards** (11)

- USP Alprazolam RS\(_{\text{USP35}}\)

©2012 The United States Pharmacopeial Convention All Rights Reserved.