Doxycycline Tablets

Type of Posting          Revision Bulletin
Posting Date            30–Mar–2018
Official Date           01–Apr–2018
Expert Committee        Chemical Medicines Monographs 1
Reason for Revision     Compliance

In accordance with the Rules and Procedures of the 2015–2020 Council of Experts, the Chemical Medicines Monographs 1 Expert Committee has revised the Doxycycline Tablets monograph. The purpose of the revision is to add Dissolution Test 2 for a generic product approved by the FDA. A Labeling section was also added.

The Doxycycline Tablets Revision Bulletin supersedes the currently official monograph. The Revision Bulletin will be incorporated in USP 42–NF 37.

Should you have any questions, please contact Praveen Pabba, Ph.D. Scientific Liaison (301-816-8540 or pkp@usp.org).
Doxycycline Tablets

**DEFINITION**
Doxycycline Tablets contain NLT 90.0% and NMT 120.0% of the labeled amount of doxycycline (C$_{22}$H$_{24}$N$_{2}$O$_{8}$).

**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**
Protect solutions containing doxycycline from light.

**Solution A:** Transfer 3.1 g of monobasic potassium phosphate, 0.5 g of edetate disodium, and 0.5 mL of triethylamine to a 1000-mL volumetric flask. Add about 850 mL of water and mix. Dilute with water to volume and adjust with 1 N sodium hydroxide to a pH of 8.5 ± 0.1.

**Solution B:** Methanol

**Mobile phase:** See Table 1.

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>Solution A (%)</th>
<th>Solution B (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.0</td>
<td>90</td>
<td>10</td>
</tr>
<tr>
<td>2.0</td>
<td>90</td>
<td>10</td>
</tr>
<tr>
<td>6.0</td>
<td>90</td>
<td>10</td>
</tr>
<tr>
<td>9.0</td>
<td>90</td>
<td>10</td>
</tr>
</tbody>
</table>

Diluent: 0.01 N hydrochloric acid

**Standard solution:** 0.12 mg/mL of USP Doxycycline Hyclate RS in Diluent. Sonicate as needed to dissolve.

**Sample solution:** Nominally 0.1 mg/mL of doxycycline from NLT 20 Tablets prepared as follows. Transfer a suitable portion of finely powdered Tablets to a suitable volumetric flask. Add 50% of the final volume of Diluent, dissolve, dilute with Diluent to volume, and mix well. Centrifuge a portion of the solution and the supernatant. [NOTE—The use of a centrifuge speed at 3,000 rpm for 10 min may be suitable.]

**Chromatographic system**
(See Chromatography (621), System Suitability.)

**Mode:** LC

**Detector:** UV 270 nm. For Identification B, a diode array detector may be used in the wavelength range of 200–400 nm.

**Column:** 2.1-mm × 5-cm; 1.7-µm packing L7. [NOTE—A 1.7-µm guard column with packing L7 was used during method validation.]

**Column temperature:** 60°C

**Flow rate:** 0.6 mL/min

**Injection volume:** 5 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

Calculate the percentage of the labeled amount of doxycycline (C$_{22}$H$_{24}$N$_{2}$O$_{8}$) in the portion of Tablets taken:

Result = (r$_{S}$/r$_{U}$) × (C$_{U}$/C$_{S}$) × P × F × 100

- r$_{U}$ = peak response from the Sample solution
- r$_{S}$ = peak response from the Standard solution
- C$_{S}$ = concentration of USP Doxycycline Hyclate RS in the Standard solution (mg/mL)
- C$_{U}$ = nominal concentration of doxycycline in the Sample solution (mg/mL)
- P = potency of doxycycline in USP Doxycycline Hyclate RS (µg/mg)
- F = conversion factor, 0.001 mg/µg

Acceptance criteria: 90.0%–120.0%

**PERFORMANCE TESTS**

**Change to read:**

- **Dissolution (711)**

  **Test 1**
  (88.3 Apr 2018)
  Medium: 0.01 N hydrochloric acid; 900 mL
  Apparatus 2: 75 rpm
  Time: 60 min
  Standard solution: 0.01 mg/mL of doxycycline from USP Doxycycline Hyclate RS in Medium
  Sample solution: Pass a portion of the solution under test through a suitable filter. Dilute a portion of the filtrate with Medium to a concentration that is similar to that of the Standard solution.

  **Instrumental conditions**
  (See Ultraviolet-Visible Spectroscopy (857).)
  Mode: UV
  Analytical wavelength: 268 nm
  Cell: 1 cm
  Blank: Medium

  **Analysis**
  Samples: Standard solution and Sample solution
  Determine the percentage of the labeled amount of doxycycline (C$_{22}$H$_{24}$N$_{2}$O$_{8}$) dissolved:

  Result = (A$_{S}$/A$_{U}$) × (C$_{L}$/L) × V × P × 100

  - A$_{S}$ = absorbance of the Sample solution
  - A$_{U}$ = absorbance of the Standard solution
  - C$_{S}$ = concentration of USP Doxycycline Hyclate RS in the Standard solution (mg/mL)
  - L = label claim (mg/Tablet)
  - V = volume of Medium, 900 mL
  - P = potency of doxycycline in USP Doxycycline Hyclate RS (µg/mg)

  **Tolerances:** NLT 85% (Q) of the labeled amount of doxycycline (C$_{22}$H$_{24}$N$_{2}$O$_{8}$) is dissolved.

  **Test 2:** If the product complies with this test, the labeling indicates that it meets USP Dissolution Test 2.
  Protect solutions containing doxycycline from light.
  Medium: 0.01 N hydrochloric acid; 900 mL
  Apparatus 2: 75 rpm
  Time: 15 min
  Standard solution: 0.01 mg/mL of doxycycline from USP Doxycycline Hyclate RS in Medium
  Sample solution: Pass a portion of the solution under test through a suitable filter. Dilute a portion of the filtrate with Medium to a concentration that is similar to that of the Standard solution.
Instrumental conditions  
(See Ultraviolet-Visible Spectroscopy (857).)  
Mode: UV  
Analytical wavelength: 268 nm  
Cell: 1 cm  
Blank: Medium  

Analysis  
Samples: Standard solution and Sample solution  
Determine the percentage of the labeled amount of doxycycline \((C_{21}H_{20}N_{2}O_{8})\) dissolved:  
\[
\text{Result} = \left( \frac{A_r}{A_s} \right) \times \left( \frac{C_s}{C_r} \right) \times D \times V \times P \times F \times 100
\]

- **Absorbance of the Sample solution**  
- **Absorbance of the Standard solution**  
- **Concentration of USP Doxycycline Hyclate RS in the Standard solution (mg/mL)**  
- **Volume of Medium, 900 mL**  
- **Potency of doxycycline in USP Doxycycline Hyclate RS (µg/mg)**  
- **Conversion factor, 0.001 mg/µg**  

Acceptance criteria: See Table 2. Disregard peaks less than 0.1%.

<table>
<thead>
<tr>
<th>Name</th>
<th>Relative Retention Time</th>
<th>Acceptance Criteria, NMT (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methacycline(^{a,b})</td>
<td>0.64</td>
<td>—</td>
</tr>
<tr>
<td>4-Epidoxycycline(^c)</td>
<td>0.79</td>
<td>1.5</td>
</tr>
<tr>
<td>Doxycycline related compound A (6-epidoxycycline)(^{d})</td>
<td>0.88</td>
<td>—</td>
</tr>
<tr>
<td>Doxycycline</td>
<td>1.0</td>
<td>—</td>
</tr>
<tr>
<td>Any individual unspecified impurity</td>
<td>—</td>
<td>0.3</td>
</tr>
<tr>
<td>Total impurities</td>
<td>—</td>
<td>2.5</td>
</tr>
</tbody>
</table>

**ADDITIONAL REQUIREMENTS**  
- **Packaging and Storage:** Preserve in tight, light-resistant containers. Store at controlled room temperature.

**Add the following:**  
- **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 Doxycycline Hyclate RS  
  - USP Doxycycline Related Compound A RS  

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[NOTE—May be available as a free base or a hydrochloride salt.]

\[ (4S, 4aR, 5S, 5aR, 6S, 12aS)-4-(Dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydronaphtacene-3,5,10,12,12a-pentahydroxy-6-methyl-1,11-dioxo-2-naphthacene-1-carboxamide. \]

\[ C_{22}H_{24}N_2O_8 \quad 444.43 \]

\[ (4S, 4aR, 5S, 5aR, 6S, 12aS)-4-(Dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydronaphtacene-3,5,10,12,12a-pentahydroxy-6-methyl-1,11-dioxo-2-naphthacene-1-carboxamide, monohydrochloride. \]

\[ C_{22}H_{24}N_2O_8 \cdot HCl \quad 480.13 \]

USP Methacycline Hydrochloride RS