Doxycycline Capsules

Type of Posting: Revision Bulletin
Posting Date: 27–Apr–2018
Official Date: 01–May–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 Capsules monograph. The purpose of the revision is to widen the limit for 4-epidoxycycline from NMT 0.35% to NMT 0.5% in the test for Organic Impurities to accommodate the sponsor’s FDA-approved specification.

The Doxycycline Capsules 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, Scientific Liaison (301-816-8540 or pkp@usp.org).
Doxycycline Capsules

DEFINITION
Doxycycline Capsules contain NLT 90.0% and NMT 120.0% of the labeled amount of doxycycline (C$_{22}$H$_{24}$N$_2$O$_6$).

IDENTIFICATION
- **A.** The UV spectrum of the major peak of the Sample solution corresponds to that of the Standard solution, as obtained in the Assay.
- **B.** 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**
  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>Table 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time (min)</td>
</tr>
<tr>
<td>0.0</td>
</tr>
<tr>
<td>2.0</td>
</tr>
<tr>
<td>4.0</td>
</tr>
<tr>
<td>6.0</td>
</tr>
<tr>
<td>9.0</td>
</tr>
</tbody>
</table>

| Diluent: | 0.01 N hydrochloric acid |
| Standard solution: | 0.12 mg/mL of USP Doxycycline Hyclate RS in Diliuent, prepared as follows. Transfer an adequate amount of doxycycline from the contents of NLT 20 Capsules to a suitable volumetric flask. Add 80% of the final volume of Diliuent, sonicate for about 5 min, shake for about 15 min, and dilute with Diliuent to volume. Centrifuge a portion of the solution for 10 min at 3000 rpm and use the supernatant for analysis. |
| Sample solution: | Nominally 0.1 mg/mL of doxycycline in Diliuent, prepared as follows. Transfer an adequate amount of doxycycline from the contents of NLT 20 Capsules to a suitable volumetric flask. Add about 268 nm |

| Analytical wavelength: | Maximum absorbance at about 268 nm |

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

**Mode:** LC

**Detector:** UV 270 nm. For Identification A, 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.

**Column temperature:** 60°

**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$_6$) in the portion of Capsules taken:

\[
\text{Result} = \left( \frac{r_d}{r_s} \right) \times \left( \frac{C_s}{C_U} \right) \times P \times F \times 100
\]

\(r_d\) = 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▲ (RB 1-Jun-2017)

**Medium:** 0.01 N hydrochloric acid; 900 mL

**Apparatus 2:** 75 rpm

**Time:** 60 min

**Standard solution:** A known concentration of USP Doxycycline Hyclate RS in Medium

**Sample solution:** Filter a portion of the solution under test and dilute with Medium, if necessary.

**Instrumental conditions**
(See Ultraviolet-Visible Spectroscopy (857).)

**Mode:** UV

**Analytical wavelength:** Maximum absorbance at about 268 nm

**Analysis**

**Samples:** Standard solution and Sample solution

Calculate the percentage of the labeled amount of doxycycline (C$_{22}$H$_{24}$N$_2$O$_6$) dissolved:

\[
\text{Result} = \left( \frac{A_s}{A_U} \right) \times \left( \frac{C_s}{C_U} \right) \times V \times P \times F \times 100
\]

\(A_s\) = 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/Capsule)

\(V\) = volume of Medium, 900 mL

\(P\) = potency of doxycycline in USP Doxycycline Hyclate RS (µg/mg)

\(F\) = conversion factor, 0.001 mg/µg

**Tolerances:** NLT 85% (Q) of the labeled amount of doxycycline (C$_{22}$H$_{24}$N$_2$O$_6$) is dissolved.

▲ Test 2

**Medium:** 0.01 N hydrochloric acid; 900 mL

**Apparatus 2:** 50 rpm, with sinkers

**Time:** 30 min

**Standard solution:** A known concentration of USP Doxycycline Hyclate RS in Medium

**Sample solution:** Filter a portion of the solution under test and dilute with Medium, if necessary.

**Instrumental conditions**
(See Ultraviolet-Visible Spectroscopy (857).)

**Mode:** UV

**Analytical wavelength:** 268 nm

**Analysis**

**Samples:** Standard solution and Sample solution
2 Doxycycline

**Change to read:**

**ADDITIONAL REQUIREMENTS**

- **Packaging and Storage:** Preserve in tight, light-resistant containers.

**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. (RB 1-Jun-2017)
- **USP Reference Standards (11)**
  - USP Doxycycline Hyclate RS
  - USP Doxycycline Related Compound A RS
    - [Note—May be available as a free base or a hydrochloride salt.]
  - USP Methacycline Hydrochloride RS

**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&lt;sup&gt;a,b&lt;/sup&gt;</td>
<td>0.64</td>
<td>—</td>
</tr>
<tr>
<td>4-epidoxycycline&lt;sup&gt;c&lt;/sup&gt;</td>
<td>0.79</td>
<td>0.5 (RB 1-May-2018)</td>
</tr>
<tr>
<td>Doxycycline related compound A</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(6-epidoxycycline)&lt;sup&gt;d&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.0</td>
<td></td>
<td>0.2</td>
</tr>
<tr>
<td>Any individual unspecified impurity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total impurities</td>
<td></td>
<td>1.0</td>
</tr>
</tbody>
</table>

<sup>a</sup> (4S,4aR,5S,5aR,12aS)-4-(Dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,5,10,12,12a-pentahydroxy-6-methylene-1,11-dioxo-2-naphthacenecarboxamide.

<sup>b</sup> Process impurities that are controlled in the drug substance are not to be reported. They are not to be included in total impurities. They are listed here for information only.

<sup>c</sup> (4R,4aR,5S,5aR,6a,12aS)-4-(Dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,5,10,12,12a-pentahydroxy-6-methyl-1,11-dioxo-2-naphthacenecarboxamide.

<sup>d</sup> (4S,4aR,5S,5aR,6S,12aS)-4-(Dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,5,10,12,12a-pentahydroxy-6-methyl-1,11-dioxo-2-naphthacenecarboxamide.