Doxycycline Hyclate Tablets

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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 Hyclate Tablets monograph. The purpose for the revision is to add Dissolution Test 3 to accommodate FDA-approved drug products with different tolerances than the existing dissolution tests.

The Doxycycline Hyclate Tablets Revision Bulletin supersedes the currently official monograph.

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

**DEFINITION**
Doxycycline Hyclate Tablets contain the equivalent of 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. INFRARED ABSORPTION** (197A)

**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 ± 0.2.

**Solution B:** Methanol

**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>0.0</td>
<td>90</td>
<td>10</td>
</tr>
<tr>
<td>2.0</td>
<td>90</td>
<td>10</td>
</tr>
<tr>
<td>4.0</td>
<td>60</td>
<td>40</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
**System suitability stock solution 1:** 1 mg/mL each of USP Doxycycline Related Compound A RS and USP Methacycline Hydrochloride RS in Diluent
**System suitability stock solution 2:** 1.2 mg/mL of USP Doxycycline Hyclate RS in Diluent
**System suitability solution:** Transfer 5 mL of System suitability stock solution 2 to a 25-mL volumetric flask, heat on a steam bath for 60 min, and evaporate to dryness on a hot plate, taking care not to char the residue. Dissolve the residue in Diluent, add 0.5 mL of System suitability stock solution 1, and dilute with Diluent to volume. Pass the solution through a suitable filter and use the filtrate.

This solution contains a mixture of 4-epidoxycycline, doxycycline related compound A, methacycline, and doxycycline. When stored in a refrigerator, this solution may be used for 14 days.

**Standard solution:** 0.3 mg/mL of USP Doxycycline Hyclate RS in Diluent. Sonicate as needed to dissolve.
**Sample solution:** Nominally 0.25 mg/mL of doxycycline in Diluent, prepared as follows. Transfer a suitable portion of NLT 20 finely powdered Tablets to a suitable volumetric flask. Add 50% of the final volume of Diluent, sonicate for about 5 min, shake for about 15 min, and dilute with Diluent to volume. Pass a portion of this solution through a suitable filter of 0.2-µm pore size.

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

**Mode:** LC
**Detector:** UV 350 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°
**Flow rate:** 0.6 mL/min
**Injection volume:** 5 µL

**System suitability**

**Samples:** System suitability solution and Standard solution [Note—See Table 2 for relative retention times.]

**Suitability requirements**

**Resolution:** NLT 1.5 between methacycline and 4-epidoxycycline; NLT 1.5 between 4-epidoxycycline and doxycycline related compound A; NLT 1.5 between doxycycline related compound A and doxycycline, System suitability solution

**Tailing factor:** NMT 1.5, Standard solution

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

**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:

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

where

- \(r_u\) = peak response from the Sample solution
- \(r_s\) = peak response from the Standard solution
- \(C_u\) = concentration of USP Doxycycline Hyclate RS in the Standard solution (mg/mL)
- \(C_s\) = nominal concentration of doxycycline in the Sample solution (mg/mL)
- \(P\) = potency of doxycycline in USP Doxycycline Hyclate RS (µg/µg)
- \(F\) = conversion factor, 0.001 mg/µg

Acceptance criteria: 90.0%–120.0%

**PERFORMANCE TESTS**

**Dissolution**

Protect solutions containing doxycycline from light.

**Test 1**

**Medium:** Water; 900 mL

**Apparatus 2:** 75 rpm, the distance between the blade and the inside bottom of the vessel being maintained at 4.5 ± 0.5 cm during the test

**Time:** 90 min

**Standard solution:** USP Doxycycline Hyclate RS in Medium

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Sample solution: Dilute with Medium, if necessary, to a concentration that is similar to the Standard solution.

Instrumental conditions
(See Ultraviolet-Visible Spectroscopy (857).)
Mode: UV-Vis
Analytical wavelength: 276 nm
Analysis
Samples: Standard solution and Sample solution
Calculate the percentage of the labeled amount of doxycycline (C$_{22}$H$_{24}$N$_2$O$_4$) dissolved:

\[
\text{Result} = \left( \frac{A_i}{A_s} \right) \times \left( \frac{C_s}{L} \right) \times V \times 100
\]

- $A_i$ = absorbance of the Sample solution
- $A_s$ = absorbance of the Standard solution
- $C_s$ = concentration of doxycycline in the Standard solution (mg/mL)
- $L$ = label claim (mg/Tablet)
- $V$ = volume of Medium, 900 mL

Tolerances: NLT 85% (Q) of the labeled amount of doxycycline (C$_{22}$H$_{24}$N$_2$O$_4$) is dissolved.

Test 2: If the product complies with this test, the labeling indicates that it meets USP Dissolution Test 2.

Medium: Water, 900 mL
Apparatus 2: 50 rpm, the distance between the blade and the inside bottom of the vessel being maintained at 4.5 ± 0.5 cm during the test
Time: 30 min

Standard solution: 22 µg/mL of doxycycline from USP Doxycycline Hyclate RS, in Medium
Sample solution: Pass a portion of the solution under test through a suitable filter.
Blank: Medium

Instrumental conditions
(See Ultraviolet-Visible Spectroscopy (857).)
Mode: UV-Vis
Analytical wavelength: 276 nm
Cell: 0.5 cm
Analysis
Samples: Standard solution and Sample solution
Calculate the percentage of the labeled amount of doxycycline (C$_{22}$H$_{24}$N$_2$O$_4$) dissolved:

\[
\text{Result} = \left( \frac{A_i}{A_s} \right) \times \left( \frac{C_s}{L} \right) \times V \times 100
\]

- $A_i$ = absorbance of the Sample solution
- $A_s$ = absorbance of the Standard solution
- $C_s$ = concentration of doxycycline in the Standard solution (mg/mL)
- $L$ = label claim (mg/Tablet)
- $V$ = volume of Medium, 900 mL

Tolerances: NLT 85% (Q) of the labeled amount of doxycycline (C$_{22}$H$_{24}$N$_2$O$_4$) is dissolved.

Test 3: If the product complies with this test, the labeling indicates that it meets USP Dissolution Test 3. Protect solutions containing doxycycline from light.

Medium: Water, 900 mL
Apparatus 2: 75 rpm
Time: 30 min

Standard solution: 0.016 mg/mL of doxycycline from USP Doxycycline Hyclate RS, in Medium. Sonicate, if necessary, in a cool water bath.

Sample solution: Pass a portion of the solution under test through a suitable filter of 0.45-µm pore size, and dilute with Medium, to a concentration that is similar to the Standard solution.

Instrumental conditions
(See Ultraviolet-Visible Spectroscopy (857).)
Mode: UV-Vis
Analytical wavelength: 276 nm
Blank: Medium
Analysis
Samples: Standard solution and Sample solution
Calculate the percentage of the labeled amount of doxycycline (C$_{22}$H$_{24}$N$_2$O$_4$) dissolved:

\[
\text{Result} = \left( \frac{A_i}{A_s} \right) \times \left( \frac{C_s}{L} \right) \times D \times V \times 100
\]

- $A_i$ = absorbance of the Sample solution
- $A_s$ = absorbance of the Standard solution
- $C_s$ = concentration of doxycycline in the Standard solution (mg/mL)
- $L$ = label claim (mg/Tablet)
- $D$ = dilution factor for the Sample solution
- $V$ = volume of Medium, 900 mL

Tolerances: NLT 80% (Q) of the labeled amount of doxycycline (C$_{22}$H$_{24}$N$_2$O$_4$) is dissolved.

• Uniformity of Dosage Units (905): Meet the requirements

IMPURITIES
• Organic impurities
Mobile phase, Diluent, System suitability solution, Sample solution, and Chromatographic system: Proceed as directed in the Assay.

Standard solution: 1.5 µg/mL of USP Doxycycline Hyclate RS in Diluent

System suitability
Samples: System suitability solution and Standard solution
Suitability requirements
Resolution: NLT 1.5 between methacycline and 4-epidoxycycline; NLT 1.5 between 4-epidoxycycline and doxycycline related compound A; NLT 1.5 between doxycycline related compound A and doxycycline, System suitability solution
Relative standard deviation: NMT 5.0% for the doxycycline peak, Standard solution

Analysis
Samples: Sample solution and Standard solution
Calculate the percentage of each impurity in the portion of Tablets taken:

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

- $r_i$ = peak response of each impurity from the Sample solution
- $r_s$ = peak response of doxycycline from the Standard solution
- $C_i$ = concentration of USP Doxycycline Hyclate RS in the Standard solution (mg/mL)
- $C_s$ = 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: See Table 2. Disregard any impurity peaks less than 0.2%.

Table 2

<table>
<thead>
<tr>
<th>Name</th>
<th>Relative Retention Time</th>
<th>Acceptance Criteria, NMT (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methacycline</td>
<td>0.64</td>
<td>—</td>
</tr>
</tbody>
</table>
Table 2 (continued)

<table>
<thead>
<tr>
<th>Name</th>
<th>Relative Retention Time</th>
<th>Acceptance Criteria, NMT (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4-Epidoxycycline</td>
<td>0.79</td>
<td>1.5</td>
</tr>
<tr>
<td>Doxycycline related compound A (6-epidoxycycline)</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>0.5</td>
</tr>
<tr>
<td>Total impurities</td>
<td>—</td>
<td>2.0</td>
</tr>
</tbody>
</table>

* Process impurities are controlled in the drug substance and are not to be reported here. They are not included in total impurities.

**ADDITIONAL REQUIREMENTS**

- **Packaging and Storage:** Preserve in tight, light-resistant containers. Store at controlled room temperature.
- **Labeling:** When more than one Dissolution test is given, the labeling states the Dissolution test used only if Test 1 is not used.
- **USP Reference Standards**
  - USP Doxycycline Hyclate RS
  - USP Doxycycline Related Compound A RS
  - USP Methacycline Hydrochloride RS

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

- \((45,4aR,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.\]  
  \(C_{22}H_{24}N_2O_8\) 444.43

- \((45,4aR,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, monohydrochloride.\]  
  \(C_{22}H_{24}N_2O_8 \cdot HCl\) 480.13

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