DDG Online Meeting: USP Proposed Chapter <1236> Solubility Measurements

11 May, 2017
Moderated by Bryan Crist
Agilent Technologies
Welcome to the DDG Online Meeting

- This is our 26th session
- Second meeting in 2017; now in our 7th year of consecutive meetings
- Worldwide users group for dissolution chemists
- Free, on-line, interactive bulletin board
- Provides annual and regional meetings around the world
- Place for practical answers to everyday questions on dissolution
DDG Mission

- The mission of the Dissolution Discussion Group (DDG) is to provide an independent forum to freely discuss the practical issues which challenge the pharmaceutical industry and affect the day-to-day task of developing, validating, and performing dissolution tests and related chemical analyses.
Welcome to the Dissolution Discussion Group (DDG) Website

The Dissolution Discussion Group (DDG) is an independent forum which gives you the opportunity to anonymously discuss issues which challenge the industry and affect the day-to-day task of developing, performing, and validating dissolution tests and related chemical analyses.

If you are new to the DDG, register today and start benefiting from a worldwide forum of dissolution professionals.

Recent News

- Replay of DDG Meeting: Concepts for Qualifying Non-Compensal Dissolution Equipment
  Recording Link: Meeting Replay
  Topic: Concepts for...
  Moderator 03-01-2017 01:26 PM

- Replay of DDG Meeting: Performance Testing of Ointments, Creams and Gels
  Recording Link: Meeting Replay
  Moderator 03-01-2017 01:25 PM

Dissolution Discussion Group (DDG)

Register Today for Free DDG Online Meetings

The Dissolution Discussion Group is pleased to present our series of free, quarterly DDG Online Meetings.

**Next Meeting Topic:** USP Proposed General Chapter <1236> Solubility Measurements
**Date/Time:** May 11th at 10:30AM EST
**Moderator Info:** Bryan Crist, Meeting Moderator, Agilent Technologies
**Duration:** 1 hour
**Registration:** Meeting Subscription Information
Previous DDG Online Meetings:

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<th>Date</th>
<th>Title</th>
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<tbody>
<tr>
<td>Feb 09, 2017</td>
<td>Concepts for Qualifying Non-Compendial Dissolution Equipment</td>
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<tr>
<td>Nov 10, 2016</td>
<td>USP Performance Testing of Ointments, Creams and Gels</td>
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<tr>
<td>May 12, 2016</td>
<td>USP &lt;1092&gt; and its Impact on Dissolution Automation</td>
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<tr>
<td>Feb 25, 2016</td>
<td>Dissolution SOP’s; Do What You Say and Say What You Do</td>
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<tr>
<td>Nov 12, 2015</td>
<td>FDA Draft Guidance; Dissolution Testing and Specifications for BCS Class 1 and 3 Drugs</td>
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<tr>
<td>Aug 13, 2015</td>
<td>Breaking Bad... Dissolution Habits</td>
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<tr>
<td>May 14, 2015</td>
<td>Crosslinking of Gelatin Capsules and Dissolution</td>
</tr>
<tr>
<td>Feb 12, 2015</td>
<td>Dissolution Method Development Considerations: Part 6 – Intrinsic Dissolution</td>
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<tr>
<td>Nov 13, 2014</td>
<td>Dissolution Method Development Considerations: Part 5 – Alcohol Induced Dose Dumping</td>
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<td>Aug 14, 2014</td>
<td>Dissolution Method Development Considerations: Part 4 – Time Point Estimation</td>
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<td>May 15, 2014</td>
<td>Dissolution Method Development Considerations: Part 3 – Challenges for Poorly Soluble Compounds</td>
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<tr>
<td>Feb 06, 2014</td>
<td>Dissolution Method Development Considerations: Part 2 – Media Volume and Sink Conditions for App 1&amp;2</td>
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<td>Nov 08, 2013</td>
<td>Dissolution Method Development Considerations: Part 1 – Filtration Requirements</td>
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<td>Aug 15, 2013</td>
<td>Operational Checks; Enhanced Mechanical Qualification Requirement - At Time of Use</td>
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<td>May 16, 2013</td>
<td>Deaeration of Dissolution Media; What’s All The Hot Air About?.</td>
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<td>Feb 14, 2013</td>
<td>Thinking Small - Challenges with Small Volume Dissolution</td>
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<td>Nov 15, 2012</td>
<td>Suggestions for the ASTM E2503-07 Dissolution Apparatus Mechanical Qualification; 5-Year Review</td>
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<tr>
<td>Aug 16, 2012</td>
<td>Use of Enzymes for Dissolution Testing of Gelatin Capsules</td>
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<tr>
<td>May 24, 2012</td>
<td>The Role of Dissolution in Quality by Design (QbD)</td>
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<td>Feb 16, 2012</td>
<td>The Dissolution Method Transfer</td>
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<td>Nov 17, 2011</td>
<td>The Dissolution Laboratory Audit</td>
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<tr>
<td>Aug 18, 2011</td>
<td>Do f1 and f2 Tell the Whole Story?</td>
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<tr>
<td>May 19, 2011</td>
<td>Best Practices for Success with the USP Dissolution Performance Verification Test (PVT)</td>
</tr>
<tr>
<td>Mar 15, 2011</td>
<td>Mechanical Calibration: ASTM vs USP; Impact of ICH on Dissolution; QBD and PAT</td>
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Today’s Panelists:

- Bryan Crist – Agilent Technologies, Inc.
- Vivian Gray – Dissolution Technologies and VA Gray Consulting
- Ken Boda – Agilent Technologies, Inc.
USP Proposed Chapter <1236>
Solubility Measurements

Discussion Points

- Terminology and Overview of USP <1236>
- Estimation of Aqueous Solubility
- Experimental Methods
- Methods for Determining Apparent Solubility
- Media Composition Tables: Human and Veterinary
Solubility

Defined in USP <1236>

The concentration limit, at thermodynamic equilibrium, to which a solute may be uniformly mixed into a solvent. This may be referred to as equilibrium (saturated) solubility to differentiate it from apparent solubility. Solubility may be stated in units of concentration such as molality, mole fraction, mole ratio, weight/volume and weight/weight.
Apparent Solubility

Defined in USP <1236>

The empirically determined solubility of a solute in a solvent system. The apparent solubility may be either higher or lower than the equilibrium solubility due to transient supersaturation or incomplete dissolution and insufficient time to reach equilibrium.
Intrinsic Solubility

Defined in USP <1236>

The solubility of the uncharged (neutral) moiety. Intrinsic solubility can only be accurately measured in pH ranges where the distribution of species is dominated by the uncharged molecule.
Dissolution, Relative to Solubility

Defined in USP <1236>

*Dissolution is the non-equilibrium process of approaching the solubility limit at thermodynamic equilibrium (i.e., the solute and solvent forming a uniformly mixed solution). The rate of dissolution will affect the time required to reach equilibrium, but will not affect the final equilibrium solubility.*
Overview

Accurate determination of the aqueous solubility of pharmaceutical materials is important for understanding both quality control and drug delivery issues for pharmaceutical formulations.

The ability to accurately measure the aqueous solubility is affected by:

- Physicochemical properties of the material
- Properties of the solubility media
- Control of solubility measurement parameters

USP <1236> Solubility Measurements, USP PF 43 (2) In-Process Revision March 2017
Aqueous Solubility Factors

Physicochemical Properties of the Material (API)

- Surface area
- Particle size
- Crystalline or amorphous structure
Aqueous Solubility Factors

Properties of the Solubility Media:

- pH
- Polarity
- Surface Tension
- Added Surfactants
- Co-Solvents
- Salts
Aqueous Solubility Factors

Control of Solubility Measurement Parameters

- Temperature
- Time
- Agitation Method
USP <1236> Solubility Measurement

Background of Solubility and Measurements:

• Thermodynamic Equilibrium and Solubility
• Methods of Estimating Aqueous Solubility
Factors Affecting Solubility and Measurements, Effects of:

- **pH** – solubility of ionizable acids and bases are pH dependent due to higher solubility of charged moiety
- **Salts and Counter-Ions** – may form salts with oppositely charged counter-ions. The solubility of a charged molecules decreases as the counter-ion increases, referred to as the “common-ion effect”
- **Co-Solvents** – water is often a poor solvent but combining with other solvents may increase solubility
- **Surfactants** – above CMC, the number of micelles in a solution increases linearly with increase of surfactant
USP <1236> Solubility Measurement

Factors Affecting Solubility and Solubility Measurements, Effects of (continued):

- **Complexing Agents** – may form complexes with low-solubility materials and enhance the solubility

- **Surface Area** – Noyes-Whitney equation. The dissolution rate of a material will not affect the equilibrium solubility, but will affect how quickly equilibrium is achieved

- **Surface Energy** (nanoparticles) – When particle size approaches the nanoparticle range, the surface energy of the particle may increase its solubility.
USP <1236> Solubility Measurement

Experimental Methods

- Saturation Shake Flask Method:
  - This method was developed over 40 years ago and is considered to be the most reliable and commonly used method today.
  - This method should be used when equilibrium solubility needs to be determined. Other methods may be used to evaluate apparent solubility, but are not considered suitable for evaluation of true equilibrium solubility.
USP <1236> Solubility Measuring

Shake Flask Method (triplicate):

- **Sample preparation**: stoppered flask with 1-2 mg/ml in excess of the estimated solubility

- Solubility may be increased by grinding prior to addition or sonication after the addition of the solid to the medium.

- **Equilibration of solution**: 24 hours minimum, temp control ±0.5°C, clarify, dilute to within range of analytical method. Saturation has been reached when multiple samples taken over time yield equivalent results.
USP <1236> Solubility Measuring

- **Analysis**: Although the solution may be analyzed by UV, HPLC is preferred because it can detect instability by resolving drug-related impurities.

- **Reporting of solubility results**: The pH of the solution should be recorded when sample is withdrawn. The excess solid should be analyzed (XRD or DSC) to verify that it has not changed. Report solubility at the final time point of consistent results ± the difference between the final two solubility measurements.
USP <1236> Solubility Measurements

Methods for Determination of Apparent Solubility

- Potentiometric Titration
- Turbidimetry (DMSO)
- Miniaturization, High-Throughput, and Automation in Solubility Measurement – necessary for using ads little compound as possible
Methods for Determination of Apparent Solubility (cont.)

- Solubility measurements in Bio-Relevant Media (at 37.0 ±0.5°C). Media composition tables for:
  - Human Fasted-State Simulated Gastric Fluid (FASSGF)
  - Human Fed-State Simulated Gastric Fluid (FESSGF)
  - Human Fasted-State Simulated Intestinal Fluid (FASSIF)
  - Human Fed-State Simulated Intestinal Fluid (FESSIF)
  - Human Simulated Colonic Fluid (SCOF)
## Human Fasted-State Simulated Gastric Fluid (FASSGF)

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Concentration (mM)</th>
<th>Concentration (mg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydrochloric acid</td>
<td>~31.3 (pH 1.6)</td>
<td>~ 1.14 (pH 1.6)</td>
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<tr>
<td>Sodium chloride</td>
<td>34.2</td>
<td>2.00</td>
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<tr>
<td>Sodium taurocholate</td>
<td>0.08</td>
<td>0.04</td>
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<tr>
<td>Lecithin</td>
<td>0.02</td>
<td>0.015</td>
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<tr>
<td>Pepsin</td>
<td>-</td>
<td>0.1</td>
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USP <1236> Solubility Measurements, USP PF 43 (2) In-Process Revision March 2017
# Human Fed-State Simulated Gastric Fluid (FESSGF)

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Concentration (mM)</th>
<th>Concentration (mg/ml)</th>
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</thead>
<tbody>
<tr>
<td>Hydrochloric acid</td>
<td>pH 5</td>
<td>pH 5</td>
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<tr>
<td>Sodium hydroxide</td>
<td>pH 5</td>
<td>pH 5</td>
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<tr>
<td>Sodium chloride</td>
<td>237.0</td>
<td>13.85</td>
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<tr>
<td>Sodium acetate</td>
<td>29.75</td>
<td>4.048</td>
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<tr>
<td>Acetic acid</td>
<td>17.12</td>
<td>1.028</td>
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<tr>
<td>Milk, whole</td>
<td>1:1</td>
<td>1:1</td>
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</table>

USP <1236> Solubility Measurements, USP PF 43 (2) In-Process Revision March 2017
Human Fasted-State Simulated Intestinal Fluid (FASSIF)

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Concentration (mM)</th>
<th>Concentration (mg/ml)</th>
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<tbody>
<tr>
<td>Maleic acid</td>
<td>19.12</td>
<td>2.219</td>
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<tr>
<td>Sodium hydroxide</td>
<td>34.8</td>
<td>1.183</td>
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<tr>
<td>Sodium chloride</td>
<td>68.6</td>
<td>4.01</td>
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<tr>
<td>Sodium taurocholate</td>
<td>3.0</td>
<td>1.7</td>
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<td>Lecithin</td>
<td>3.0</td>
<td>0.15</td>
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USP <1236> Solubility Measurements, USP PF 43 (2) In-Process Revision March 2017
## Human Fed-State Simulated Intestinal Fluid (FESSIF)

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Concentration (mM)</th>
<th>Concentration (mg/ml)</th>
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</thead>
<tbody>
<tr>
<td>Maleic acid</td>
<td>55.02</td>
<td>2.77g</td>
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<tr>
<td>Sodium hydroxide</td>
<td>81.65</td>
<td>6.386</td>
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<tr>
<td>Sodium chloride</td>
<td>125.5</td>
<td>7.334</td>
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<td>Sodium taurocholate</td>
<td>10</td>
<td>5.5</td>
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<tr>
<td>Lecithin</td>
<td>2.0</td>
<td>1.5</td>
</tr>
<tr>
<td>Glyceryl monostearate</td>
<td>5.0</td>
<td>1.8</td>
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<tr>
<td>Sodium oleate</td>
<td>0.8</td>
<td>0.24</td>
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# Human Simulated Colonic Fluid (SCOF2)

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Concentration (mM)</th>
<th>Concentration (mg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium hydroxide</td>
<td>~159 (pH 5.8)</td>
<td>~5.4 (pH 5.8)</td>
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<tr>
<td>Acetic acid, glacial</td>
<td>170</td>
<td>10.2</td>
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</table>
Other Simulated Veterinary Fluids

• Canine Fasted-State Simulated Gastric Fluid (FASSGFC)
  • FASSGFC pH 1.2-2.5
  • FASSGFC pH 2.5-6.5

• Canine Fasted-State Simulated Intestinal Fluid (FASSIFC)

• Bovine (at 39°C):
  • pH 2.5
  • pH 3.5
  • pH 5.0
  • pH 6.8 (with and without short-chain fatty acids)
Comment Period for <1236>

Comment Deadline: May 31, 2017
General Discussion

USP PROPOSED CHAPTER <1236>
SOLUBILITY MEASUREMENTS
References

- United States Pharmacopoeial Convention, Inc. United States Pharmacopeia (USP 40-NF 35). Rockville(MD); 2017:
  - <711> Dissolution

- United States Pharmacopeial Forum, <1236> Solubility Measurements, USP PF 43 (2) In-Process Revision, March 2017
Suggestions for Future Meetings?

Mark your calendars for the next Online DDG meeting: Thursday, 10 August, 2017. Topic to be announced.

We look for your suggestions for current hot topics in the field of dissolution such as drug release from novel dosage forms, FDA Guidance, Apparatus Qualification, etc. We do want to hear from you so please continue to suggest topics on the DDG site.

Meetings are held quarterly on Tuesdays from 10:30-11:30 Eastern US Time. Please consult the DDG site for recorded sessions, future topics and updated information.
Thank you to our panelists, your comments, and your participation!

www.dissolution.com