Issues in Compound Storage in DMSO

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Lipinski SBS, Hague 2002
Sample storage in DMSO - overview

Centralized storage
Business rules enforced
Long storage times

End user handling / storage
No business rules / chaotic
Short storage times

solubility
chemical stability

solubility
chemical stability

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Sample lifetime. What is the key issue?

- Compound disappears from DMSO solution

- What is the explanation?

- Chemical integrity
  - Keep cold and frozen
  - Avoid oxygen
  - Keep dry

- Compound solubility
  - Cold and / or frozen is the worst choice possible
  - Avoid freeze thaw cycles
Chemical integrity / solubility balance

- Chris Lipinski’s personal opinion
  - Reasonable people might disagree

- Solubility / precipitation is a bigger problem than chemical integrity

- Solubility is the major problem for end users
  - Short term handling / storage

- Major positive impact is possible with end users
  - People issue not a technology issue

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Where do compounds come from?

- **Legacy compounds are less chemically stable**
  - Traditional medicinal chemistry
    - Good chemistry control of conditions
    - Poorer stability compounds can be isolated
    - E.g. beta lactams

- **Combinatorial chemistry**
  - Poorer chemistry control of conditions
    - Stable compounds tend to be isolated

- **Caveat – combinatorial chemistry**
  - Acidic hydrolysis due to HPLC additives
    - Trifluoroacetic acid, formic acid
Compound Solubility in DMSO

- Compound solubility is determined by 2 factors:
  - Solvation energy and crystal disruption

- Continuum in the importance of each

- Low melting point lipophilic compound
  - Solvation most important

- High melting point hydrophilic compound
  - Crystal disruption most important
DMSO Really Helps Solvation

- Compound has to make a “hole” in DMSO to dissolve
- Easier to do this in DMSO than in water
  - No H-bond donor / acceptor networks to disrupt
- DMSO has a high dielectric constant
- Solvates compound dipoles
  - Almost all drugs have dipoles
- DMSO doesn’t solvate hydrocarbons
  - E.g. hexane is immiscible in DMSO
DMSO – water phase diagram

DMSO containing 9% water is unfrozen in the typical lab refrigerator

Very bad practice. Typical biology procedure of storing samples in DMSO in the non-freezer part of a lab refrigerator

Nature (1969), 220, 1315-1317

Lipinski SBS, Hague 2002
Compounds Differ in DMSO Solubility Based on Crystalline Form

- Oswald’s “Rule of Stages”

- Sequence of compound batch isolation proceeds towards thermodynamically most stable form
  1. Amorphous – highest energy solid form
  2. Highest energy crystalline polymorph
  3. Lowest energy crystalline polymorph

- Amorphous is the highest energy form
  - Most soluble in DMSO
  - Lowest melting point
Timing Factor in Compound DMSO Solubility

- Once a compound crystallizes from DNSO it will not easily re-dissolve
  - Crystallized compound is in a lower energy less DMSO soluble form

- Narrow working window (time window) for keeping most compounds dissolved in DMSO
  - 1 to 2 days at room temperature
  - Explains why compounds are active when freshly made but not when stored

- Freeze thaw cycles increase the probability of crystallization
Vials of 60 mM compound in MDSO at room temperature are visually checked the morning after the aqueous solubility assay is completed.
Compound Insolubility at 60 mM in DMSO

- Non combinatorial compounds
- Traditional medchem synthesis
- Solubility test using 60 mM DMSO stock solution
- 6% insoluble at 60 mM in DMSO
  - Cpdds dissolved at 60 mM in DMSO
  - Vials checked for pptn at rt 24 hr post dissolving
  - 2381 / 40000 were insoluble

- Underestimates DMSO solubility problem
  - Because least aqueous soluble were excluded
Visual precipitation detection is impossible for compounds in DMSO distributed in this format
DMSO Solubility Data Source

www.gaylordchem.com

Solubility of Active Pharmaceutical Compounds (APCs) in USP grade Dimethyl Sulfoxide (DMSO)

Lipinski SBS, Hague 2002
# Solubilities of Active Pharmaceuticals Compounds in Dimethyl Sulfoxide

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<th>Pharmaceutical Nomenclature</th>
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<th>g/100g DMSO@25°C</th>
<th>g/100g solution@25°C</th>
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Capturing Gaylord Solubility Data

- Save web pages as Adobe PDF file
- Open PDF file with Adobe Acrobat
- Select table with Acrobat text table tool
- Copy table to clipboard
- Paste to Accord for Excel
- Merge in structures from SciFinder, Isisbase

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Live chemistry structures can be used in calculations

Lipinski SBS, Hague 2002
Parsing Compounds with DMSO solubility

- 107 compounds with DMSO solubility
  - Remove salts
  - Remove organo-metallics
  - Remove cpds with no structure
  - Remove cpds with zero DMSO solubility
  - Remove cpds without melting points

- 57 compounds for analysis
Parsing Compounds with DMSO solubility

Melting point from Merck Index. Highest polymorph value used. Lower value in range used if a range was reported.
Some compounds with zero DMSO solubility

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More compounds with zero DMSO solubility

<table>
<thead>
<tr>
<th>Compound</th>
<th>Structure</th>
<th>DMSO Solubility</th>
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Will be glad to forward entire solubility data set in machine readable format upon request

Christopher_A_Lipinski@Groton.Pfizer.Com
DMSO solubility for 68 cpds v.s. 24 calculations

Nothing useful observed in this data set
Calculating Oxidative Chemical Stability

Syracuse Research Corporation Aopwin software, free download from:

http://www.epa.gov/oppt/exposure/docs/episuitedl.htm

Lipinski SBS, Hague 2002