Stability of Parenteral Drug Products

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Outline

• General Overview
• Small vs. Large Molecule Stability
  • Small molecules
  • Proteins
• Small molecule chemistry
• Protein stability issues
• Packaging
• Accelerating Degradation
• Conclusions
Background

- Marketed pharmaceutical products need to specify shelf-life under storage conditions
  - Assure safety
  - Assure potency/activity
  - Have no obvious visual changes
    - Precipitation
    - Discoloration
- **Shelf-life set by what hits its limit first!**
# ICH Climatic Zones

<table>
<thead>
<tr>
<th>Zone</th>
<th>Climate</th>
<th>Temperature</th>
<th>%RH</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Temperate</td>
<td>21°C</td>
<td>45%</td>
</tr>
<tr>
<td>II</td>
<td>Subtropical</td>
<td>25°C</td>
<td>60%</td>
</tr>
<tr>
<td>III</td>
<td>Hot dry</td>
<td>30°C</td>
<td>35%</td>
</tr>
<tr>
<td>IVa</td>
<td>Hot, humid</td>
<td>30°C</td>
<td>65%</td>
</tr>
<tr>
<td>IVb</td>
<td>Hot, very humid</td>
<td>30°C</td>
<td>75%</td>
</tr>
</tbody>
</table>

Many parenterals are stored refrigerated: 5-8°C
Safety

• Degradation products of a drug are a potential safety risk
• Lower risk if degradants identified
  • Metabolites generally low risk
  • Qualification of degradants based on defaults (typically 0.2-0.5% of active) or safety data
  • Compounds with genotoxic risk are more tightly regulated
• Microbial count needs to remain acceptable at end of shelf-life
  • Monitor preservative levels
Potency

- Drug product needs to remain active at the end of its shelf-life (typically, >85% of label claim)
  - Loss of activity can be due to physical changes, e.g., precipitation
  - Loss can be due to chemical degradation
  - Variability can play big role (may have differences between unit doses)
Small Molecule vs. Protein Stability

**Small Molecules**
- Loss of potency by any molecular change
- Only concerned with primary structure
- Most shelf-life limited by formation of low levels of degradants
- Arrhenius behavior in solution; modified Arrhenius (ASAP) in solid

**Proteins**
- Some bond changes may not impact activity
- Small changes in structure can have a large impact on activity
- Concerned with 1°, 2°, 3° and 4° structures
- Multiple reversible and irreversible steps make Arrhenius behavior difficult to see even in solution
Small Molecule Degradation Chemistry

- Hydrolysis
  - Esters, amides
- Oxidation
  - Amines, sulfides
- Reaction with excipients, impurities
  - Maillard (amines + sugars), reactions with peroxides, formaldehyde
- Rearrangements
  - Lactonization, lactamization
Hydrolyses Generally pH-Dependent
Oxidation: Classic Reaction with Oxygen
Oxidation of Electron-Rich Species

Oxidation slower at low pH

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Antioxidants

- Oxidations can be controlled by antioxidants (e.g., BHT, BHA)
- Oxidation can be fast once antioxidant is consumed
  - Need to monitor antioxidant levels with time
Accelerated Aging: Small Molecule Solutions

- Chemical Stability (Including Antioxidants/Preservatives)
  - Generally follows Arrhenius behavior
  - Temperatures close to 100°C have low oxygen and may not be predictive
  - Change in pH with temperature may need to be accounted for

- Physical Stability
  - Precipitation can be accelerated using heat cycling
  - Loss of stabilizers to diffusion into packaging generally follows Arrhenius behavior, but complicated by solubility changes with temperature
Small Molecule Accelerated Stability

0 100 200 300 400 500 600

0 1 2 3 4 5 6 7 8 9 10 11 12 13 14

%Degradant

Relative Time

Low Temperature

High Temperature

Same curvature independent of T
Accelerated Stability: Traditional Approach

60 Days at low or high T

$k \leq k$ to specification limit

$k \ll k$ to specification limit
ASAP: Accelerated Stability Assessment Program (Isoconversion)

ASAP approach: % degradant fixed at specification limit, time adjusted as needed
Accelerated Stability: Traditional Arrhenius Approach

Predicted Shelf Life (traditional approach) 0.5 yrs
Experimental Shelf Life 1.2 yrs

Historical method: high T deviations give non-linear behavior

Real time data

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CP-456,773/60%RH
Accelerated Stability: ASAP Approach

Predicted Shelf Life (ASAP/isoconversion) 1.2 yrs
Experimental Shelf Life 1.2 yrs

Real time data

CP-456,773/60%RH
# Impact of Activation Energy on Accelerated Stability Studies

<table>
<thead>
<tr>
<th>$E_a$ (kcal/mol)</th>
<th>40°C</th>
<th>60°C</th>
<th>80°C</th>
</tr>
</thead>
<tbody>
<tr>
<td>12 Low activation energy</td>
<td>58</td>
<td>24</td>
<td>14</td>
</tr>
<tr>
<td>29 Average activation energy</td>
<td>18</td>
<td>1</td>
<td>0.3</td>
</tr>
<tr>
<td>39 High activation energy</td>
<td>6.5</td>
<td>0.1</td>
<td>0.01</td>
</tr>
</tbody>
</table>
Accelerated Aging: Small Molecule Solids (Lyophiles)

Humidity Corrected Arrhenius Equation

\[ \ln k = \ln A - \frac{E_a}{(RT)} + B(\%RH) \]

Typically lyophiles are at <15\% RH: equation still applies
Accelerated Stability Assessment Program (ASAP)

Note: RH dependence does not imply hydrolyses
Error Bars in Accelerated Aging

Example: Confidence Interval
For 2 year shelf life (25°C/60%RH) = 95%
For 3 year shelf life (25°C/60%RH) = 75%

Can be calculated using ASAPprime™
Typical $E_a$ and $B$ values (n=60)
Protein Unfolding

Folded “native” protein: Active Form

Unfolded protein: Inactive Form
Protein Denaturation

4°-Structure
- Subunits dissociated
- Subunits disrupted

3°-Structure
- Covalent interactions disrupted between amino acid side chains
- Dipole-dipole interactions between amino acid side-chains with themselves and solvent disrupted
- Van der Waals interactions disrupted between nonpolar amino acid side-chains

2°-Structure
- Loss of repeat patterns (α-helices, β-sheets)

1°-Structure
- Not impacted
Protein Inactivation

\[ \text{N} \xrightleftharpoons[k_1]{k_{-1}} \text{U} \xrightarrow{k_2} \text{D} \]

N = native \quad K = \frac{k_1}{k_{-1}} = \exp(-\Delta G/RT)
U = unfolded
D = denatured \quad K = 1 \quad \text{when } T = T_m
Packaging

• Solids
  • Mostly concerned with moisture protection; RH as a function of time
  • Can be predicted accurately (ASAP\textsuperscript{TM}) prime

• Solutions
  • Packaging (container, closures) more integral to stability
  • Concerned with materials leaching from packaging
  • Concerned with loss of stabilizers into packaging
  • Packaging can bring catalysts into solution (even glass)
Conclusions

• Stability is a major part of drug product development
• Small molecule and large molecule drugs have different factors affecting their stability
• Accelerated stability is well-developed with small molecules, but remains challenging with large molecules
• Packaging must be considered in all stability assessments