Case Study 2: Precipitation on Injection – Problem Solving Failure

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Precipitation on Injection: Problem Statement

**Clinical program halted**
- Clinical dose escalation limited by injection site reaction
- Exposure not linear with increasing dose in human

**Reformulate to proceed forward**
- Significant work already done to evaluate improved formulations
Bioavailability

- Not determined in humans
- Rodent study conducted to evaluate
  - Conducted and observed <10% bioavailability
  - Concentration effect on exposure

Reformulation work suggested an excipient that may help

- Concern for concentrations needed
- Concern over approvability of excipient – not in many formulations
Bioavailability for Most Biologics > 50%

Fig. 3. Relationship between systemic availability of biotherapeutics and their molecular weight in various species. The data are provided in Tables I and II

WFRichter et al AAPS Journal 2012 14 (3) 559-570

SC BA > 50%
For most drugs
Higher Levels of Excipient Improve Biocompatibility

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Precipitation on Injection
Poloxamer 407 has similar effect and is in commercial product.

5% Poloxamer 407 doubles solubility vs. 5% Solutol.

* has specific formulation: PVP mixed in acetic acid with peptide first, then spiked with polysorbate 20.
** All Polysorbate 20 formulations are based on volume percent not (weight/volume) percentage.
Poloxamer 188 also helps
Plasma Compatibility Useful for Screening Aqueous Miscible Formulations

### In Vitro Turbidity Assay

<table>
<thead>
<tr>
<th>mg/mL</th>
<th>% solutol</th>
<th>2% P407</th>
<th>2% P407 Plasma</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>0.7</td>
<td>0.7</td>
<td>0.7</td>
</tr>
<tr>
<td>4</td>
<td>1.2</td>
<td>1.1</td>
<td>1.4</td>
</tr>
<tr>
<td>8</td>
<td>1.7</td>
<td>0.3</td>
<td>1.4</td>
</tr>
<tr>
<td>10</td>
<td>1.9</td>
<td>0.5</td>
<td>1.4</td>
</tr>
<tr>
<td>12</td>
<td>1.9</td>
<td>0.8</td>
<td>1.6</td>
</tr>
</tbody>
</table>

Relative to current formulation:
- **Better**
- **No improvement**
- **Worse**

### Bioavailability in rat PK study at 10 mg/kg

<table>
<thead>
<tr>
<th>mg/mL</th>
<th>% solutol</th>
<th>2% P407</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>6%</td>
<td>14%</td>
</tr>
<tr>
<td>4</td>
<td>5%</td>
<td>9%</td>
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<tr>
<td>8</td>
<td>3%</td>
<td>7%</td>
</tr>
<tr>
<td>10</td>
<td>3%</td>
<td>6%</td>
</tr>
<tr>
<td>12</td>
<td>2%</td>
<td>4%</td>
</tr>
</tbody>
</table>

NOTE: *25% solutol solns showed reduced Peptide conc: 2.2, 5.3, 6.4, 7.3 mg/ml

BA improved at 2 mg/ml
Conclusion: Failure

Problem considered too difficult to solve in the short term
And may be insoluble or non-solvable

Program discontinued
References for solubilization

Can be obtained on the BASF website:

**Solubility Enhancement with BASF Pharma Polymers**
Solubilizer Compendium
Thomas Reintjes
October 2011

**Pharmaceutical Technology of BASF Excipients**
Volker Buhler
June 2008

_Solubilizing Excipients in Oral and Injectable Formulations_
Strickley, Robert G
_Pharmaceutical Research;_ Feb 2004; 21, 2; ProQuest Central
pg. 201
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