Pharmaceutical Preformulation

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Preformulation:
- a stage of development during which the physicochemical properties of drug substance are characterized

Some commonly evaluated parameters:
- Solubility
- Dissolution behavior
- Stability
- Partition coefficient
- Ionization constant (pKa)
- Solid state properties such as crystal forms/polymorphs, water sorption behavior, surface properties, particle size and shape, and other mechanical properties, et. al.
Why is Preformulation Important?

“It is a capital mistake to theorize before one has data”
- *Scandal in Bohemia*, Sir Arthur Conan Doyle

- Thorough preformulation work is the foundation of developing robust formulations.
There are critical differences between companies at the detailed level of knowledge and their ability to learn before doing

- knowledge of the underlying variables and their relationship to performance
- knowledge of the future manufacturing environment and the new variables introduced by that environment

• Preformulation
  – A case of learning before doing
Preformulation in the Overall R&D Process

Hit validation and lead selection

Lead optimization

Candidate selection process

Preparation for and completion of PoC Study(ies)

3 months to 6 months

6 months to 24 months

3 months to 9 months

12 months to 24 months

Preformulation
Solubility

- Importance of solubility

- Theoretical and practical considerations in solubility determination
• Drug candidates are becoming more lipophilic and poorly soluble
- Recent trends in aqueous solubility of discovery compounds
Formulation Challenges with Poorly Soluble Compounds

- Poor dissolution rate
- Low and variable bioavailability
- More potential for food effect
- Inability to deliver high doses for tox studies
- Difficulty in developing parenteral formulations
Drug has to be in solution to be absorbed!

- Tablet or capsule → Disintegration → Granules or aggregates
- Granules or aggregates → Deaggregation → Fine Particle
- Dissolution of Fine Particle → Precipitation
- Drug in solution
- Dissolution → Fine fine particle
- Absorption → Systemic circulation
Solubility Criteria: how soluble is soluble enough?

- Dependent on dose and permeability
  - Dissolution time
  - Maximum Absorbable Dose (MAD):
    \[ S \text{ (mg/mL)} \times \text{Ka (min)} \times \text{SIWV (mL)} \times \text{SITT (min)} \]

- Biopharmaceutical Classification
**Biopharmaceutics Classification System (BCS)**

### Classification

- **Class I**  High Permeability, High Solubility
- **Class II** High Permeability, Low Solubility
- **Class III** Low Permeability, High Solubility
- **Class IV** Low Permeability, Low Solubility

### Class Boundaries

- **Highly soluble**: the highest dose is soluble in <250 ml water over a pH range of 1 to 7.5
- **Highly permeable**: >90% dose absorbed in humans
- **Rapidly dissolving**: >85% of labeled amount of drug substance dissolves within 30 minutes
Solubility and Bioavailability

● **Dissolution rate limited absorption**
  – The absolute amount of drug absorbed increases with the increasing of the dose
  – Reduce particle size and using solution formulation should enhance absorption

● **Solubility limited absorption**
  – The absolute amount of drug absorbed does not increase with the increasing of the dose
  – Increasing dissolution rate does not increase absorption
Solvents for Solubility Studies

- **For developability assessment:**
  - Simulated gastric fluid (SGF)
  - Simulated intestinal fluid (SIF)
  - pH 7.4 buffer
  - Intrinsic solubility to estimate pH-solubility profile

- **For Formulation Development:**
  - pH solubility profile
  - Solubility in solubilization agents/systems
    - Co-solvents
    - Surfactants
    - Complexation agents
    - Combinations of techniques
Factors Causing Poor Solubility

- High crystallinity/high MP
  - Zwitterion formation
  - Insoluble salts
  - H-bonding networks

- Hydrophobicity/High LogP
  - Lack of ionizable groups
  - High molecular weight
**Effect of Solid State Form**

- **Amorphous vs. crystalline**
  - Differences could be > 1000x

- **Polymorphs**

<table>
<thead>
<tr>
<th>Equilibration Time (Days)</th>
<th>Solubility (mcg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1200</td>
</tr>
<tr>
<td>2</td>
<td>1000</td>
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<tr>
<td>3</td>
<td>800</td>
</tr>
<tr>
<td>4</td>
<td>600</td>
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<td>5</td>
<td>400</td>
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<td>6</td>
<td>200</td>
</tr>
<tr>
<td>7</td>
<td>100</td>
</tr>
<tr>
<td>8</td>
<td>50</td>
</tr>
<tr>
<td>9</td>
<td>10</td>
</tr>
</tbody>
</table>

Equilibration Time (Days)
**Examples**

Comparison of apparent solubility of amorphous material (A) and crystalline material (C):

<table>
<thead>
<tr>
<th>Solvent</th>
<th>Solute</th>
<th>Melting Point (°C)</th>
<th>Solubility Ratio (A/C)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Caffeine</td>
<td>238</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>Theophylline</td>
<td>272</td>
<td>50</td>
</tr>
<tr>
<td></td>
<td>Morphine</td>
<td>197</td>
<td>270</td>
</tr>
<tr>
<td></td>
<td>Hydrochlorthiazide</td>
<td>273</td>
<td>1.1</td>
</tr>
<tr>
<td></td>
<td>Sulfamethoxydiazine</td>
<td>215</td>
<td>1.5</td>
</tr>
</tbody>
</table>

*S. Yalkowsky, Solubility and Solubilization in Aqueous Media, American Chemical Society, Washington D.C. (1999).*
Examples

Comparison of apparent solubility of polymorphs:

<table>
<thead>
<tr>
<th>Solute</th>
<th>Δ Melting Point (°C)</th>
<th>Solubility Ratio (L/H)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acemetacin</td>
<td>20</td>
<td>2.3</td>
</tr>
<tr>
<td></td>
<td>70</td>
<td>4.7</td>
</tr>
<tr>
<td>Cyclopenthiazide</td>
<td>41</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>57</td>
<td>3.6</td>
</tr>
<tr>
<td>Mebendazole</td>
<td>30</td>
<td>3.6</td>
</tr>
<tr>
<td></td>
<td>70</td>
<td>7.4</td>
</tr>
<tr>
<td>Spironolactone</td>
<td>05</td>
<td>1.2</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>1.9</td>
</tr>
</tbody>
</table>

*S. Yalkowsky, Solubility and Solubilization in Aqueous Media, American Chemical Society, Washington D.C. (1999).*
- Definition of solubility
  - Molarity of the substance in a solution that is at chemical equilibrium with an excess of the undissolved substance

- What is kinetic/non-equilibrium solubility?
Effect of intrinsic solubility on the shape of the pH-solubility profile:

Effect of temperature
Challenges with weak acid or base
- pH of the saturated solution vs. pHmax
- It is only from a solubility experiment at a pH below pHmax that the solubility of the salt of a weak base can be estimated.

Different salts will have different solubility in non-aqueous systems.
• Importance of Dissolution

• Theoretical and practical considerations in dissolution rate determination
Dissolution rate for poorly soluble compounds may often be the rate limiting step to absorption.

Examples of drugs with dissolution rate limited absorption:
- Digoxin
- Penicillin V
- Phenytoin
- Quinidine
- Tetracyclines
Factors Affecting Dissolution Rate

- $\frac{DC}{Dt} = kd (Cs - C) = KiA/V (Cs-C)$
  - $kd$ dissolution rate constant
  - $Ki$ intrinsic dissolution rate constant
- Volume of the dissolution medium: dose:solubility ratio
- Intrinsic dissolution rate constant: using rotating disk apparatus
- Surface area of the solid
  - particle size effect
  - Effective surface area: the portion in actual contact with the dissolution medium
Choice of Dissolution Medium

- Biorelevant dissolution media should be the most important consideration:
  - USP SGF (USP 2000)
  - USP SIF (USP 2000)
  - Simulated Gastric Fluid-fasted state
  - Simulated Intestinal Fluid-fasted state
  - Simulated intestinal Fluid-fed state
  - Surfactant such Sodium Lauryl Sulfate (SLS)
  - Milk

- IVIVC: which comes first?
**Dissolution Rate and Salt Selection**

- **What really happen in the gut?**
  - Higher dissolution rate in the gut for soluble salts
  - Super-saturation possibility
  - Importance of knowing the solubility of the HCl salt
  - Potential negative impacts by salts:
    - Higher degradation
    - Conversion to free base on the surface – impact on the dissolution of the remaining salts
    - Potential toxicity

- **Effect of salts on solubility in solubilization systems**
Stability

- Importance of stability

- Theoretical and practical considerations in stability determination
Chemical Stability

- In SGF and SIF
- pH-stability profile
- Solid state stability
  - Effect of moisture
  - Effect of solid state form – amorphous vs. crystalline
- Excipient compatibility
  - Effect of moisture
  - Effect of processing
- Degradation mechanism
  - Hydrolysis
  - Oxidation potential
  - Effect of temperature
Physical Stability

- Characterization of Amorphous Material
  - Tg and mobility
  - Effect of moisture on Tg
  - Solid solubility
- Characterization of hydrates/solvates
  - Effect of processing
  - Impact on chemical stability and bioavailability
Solid State Properties

- Importance of Solid State Properties

- Theoretical and practical considerations in solid state characterization
Impact on Pharmaceutical Properties

- Bioavailability (solubility/dissolution rate)
- Stability (physical and chemical)
- Processing Factors
  - Hygroscopicity
  - Bulk, mechanical, and rheological properties
  - Ease of isolation, filtration, and drying
  - Degree of purification
The Fundamental Question:

What will be the consequence should a new thermodynamically more stable form is discovered?

- **High risk** if this could lead to significant delay in the overall project timeline or product failure

- **Low risk** if impact on timeline and resources are minimum
High Risk Compounds

- Poorly soluble compounds as defined by the FDA biopharmaceutical classification system:
  \[
  \text{Solubility in pH 1-8 solutions x 250 mL} < \text{Dose}
  \]

- Compounds that would require one of the non-equilibrium methods or semi-solid/liquid formulations to enhance dissolution rate/bioavailability
  - amorphous
  - meta-stable polymorphs
  - solid dispersion
  - lipid based formulations

- Compounds with parenteral formulations formulated close to equilibrium solubilities at given temperature
Potential Risks Due to Salt or Form Changes

- **Additional Studies Required Due to Salt and/or Form Changes**
  - PK bridging studies
  - Repeated tox (1 month or 3 months)
  - Additional considerations due to potential impurity changes
  - Bio-equivalent studies

- **Risk Associated with Developability Assessment of Drug Candidate**
  - Impact on tox formulation
  - Impact on bioavailability at clinically relevant doses
Patent Protection for Potential LCM Opportunities

- Compound Claimed: 1990
- Product Lunch: 2001
- Patent expired: 2010
- Extension: 2015

Original API

PTR:

Salts and Polymorphs

Polymorphs/Salts Claimed: 1998

Generic Entry for All Other Forms not Covered

PTR: Patent Term Restoration = half of the investigational period + all of the FDA review period
Balancing Various Factors:
- Physical stability: the thermodynamically most stable form is always the preferred choice
- Bioavailability: clinically relevant doses vs. tox coverage
- Process consideration
- Other physicochemical properties such as hygroscopicity, morphology and chemical stability

Salt Selection vs. Form Selection
- An integrated process
Some Practical Considerations in Salt Screening and Selection

- **Dosage Form Considerations**
  - IV vs. oral formulations
  - High dose vs. low dose
  - Excipient compatibility
  - Interaction with other actives in potential combination formulations

- **Salts and Other Solubilization Techniques**
  - Effect of Salts on Complexation Binding Constants
  - Effect of Salts on Solubilization by Surfactants
  - Solubility of Salts in Non-aqueous Solvents

- **Toxicological Considerations**
Some Product Specific Aspects

- **Solid dosage forms**
  - Effect of micronization and processing such as granulation on solid state properties and chemical stability
  - Effect of excipients on crystallization/nucleation
  - Powder flow properties: bulk density, compression properties and particle size and shapes

- **Parenteral Dosage Forms**
  - Injection site precipitation
  - Pain upon injection
  - Toxicity of new excipients
  - Effect of excipients on crystallization/nucleation

- **Suspensions**
  - Effect of processing and formulation on the physical and chemical stability
  - Effect of excipients on crystallization/nucleation
• Automation of Common Preformulation Studies:
  – Solubility as a function of pH and composition
  – Solution stability as a function of pH and composition
  – Excipient compatibility studies
  – Others
Example: Platform for Excipient Compatibility Studies

- **Balance**
- **10x10 custom block**
  - Removable custom blocks (holding 100 20 ml vials each)
- **10x10 custom block**
- **Robotic arm changing Station**
  - Moved at (hrs) 1, 24, 72, 168 for each pH
- **Block 1: 20°C**
- **Block 2: 45°C**
- **Block 3: 35°C**
- **Block 4: 25°C**
- **Block 5: 5°C**

**Interactive HPLC assay**: Undiluted sample tested first, rejected or accepted based on area cutoff set by user calibration curve run prior to starting, if rejected instrument dilutes (10x, 100x, or 1000x) and then rerun.

User removes blocks from Platform and separates samples and places them on stability. Stability plates can be run on system.
Final Thoughts

- Thorough preformulation work is the foundation of developing robust formulations.
- Pay now or pay later is a balancing act.
- Organization structures vary, but the science doesn’t.
- Good science is always the right thing to do!


