Challenges and Opportunities for Oral Delivery of Poorly Soluble Drugs

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Outline

• Overview of Industry Today
  – Sources of Oral Bioavailability Limitations
  – Market Trends

• Challenges & Opportunities for Poorly Soluble APIs
  – Impact of low solubility in development
  – Case studies of successful development

• Technologies and Limitations for Handling Poorly Soluble Compounds
  – Emerging Opportunities to Improve Amorphous Development

• Future Direction and Concluding Comments
Sources of Bioavailability Limitations

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Solubility Trends & Developmental Pipelines

Compound Trends

Lipinski’s Rule of 5

- Predictor of Limited Oral Bioavailability
  - Molecular Weight > 500
  - Log P > 5
  - H-Bond Donors > 5
  - H-Bond Acceptors > 10

- Examples Meeting The Rule of 5
  - Cyclosporine
  - Itraconazole
  - Ritonavir
  - Lopinavir

592 oral drugs approved worldwide between 1983 and 2007

The size of the squares represents the mean Lipinski score
Low solubility drug development challenges

- Low solubility can present major challenges to the successful development of NCEs
- The nature of the challenges change as the program progresses through clinical development
Solubility Driven Challenges in Preclinical Development

- Adequate solubility needed for potency and safety assays and must be considered during design and execution of *in vitro* assays
  - Compounds with poor solubility have the potential to precipitate in assay media/buffer.
  - DMSO stock solutions of poorly soluble compounds have the potential to precipitate during freeze-thaw cycles.
  - Assay media greatly impacts solubility

- Adequate solubility is needed for *in vivo* studies at all stages leading to EIH
  - To achieve optimal exposure in PK/PD studies to get proof of concept (POC) in appropriate animal models for project to move to the next stage
  - Multiple fold exposure is required for safety studies in preclinical tox species
  - Salt forms or special formulation are needed to achieve the desired exposure
  - To achieve the exposure in human studies

- Future Challenges
  - Design and development of technologies and compositions to support early development work with limited API supply
  - Optimization of in silico methods to improve computer based design
  - New materials for achieving maximum exposure (multiples over anticipated dose)
Options for Improving Solubility

Low solubility compounds are inherently more challenging to develop, raising the risk of failure.

Many technologies can address low solubility but also present trade-offs.
Current Success Stories

Tricor® - Formulation Intervention to Improve Delivery

200 mg Capsule
- Milled fenofibrate

160 mg Tablet
- Micronized fenofibrate

145 mg Tablet
- NanoCrystal fenofibrate

![Graphs showing absorption and bioavailability comparisons for different formulations.]
Current Success Stories

**Neoral® - Formulation Intervention to Improve Delivery and Extend Market Protection**

![Neoral® Tablets](image)

**Before**

![API Tablets](image)

**After Dilution**

![Sandimmune™ Tablets](image)

![Neoral™ Tablets](image)

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**Figure 1** — Interindividual comparison of cyclosporine concentration–time profiles following single oral administration of 300-mg reference formulation to 24 volunteers. Inset shows the initial portion of the profile on a linear–linear scale.

**Figure 2** — Interindividual comparison of cyclosporine concentration–time profiles following single oral administration of 150-mg test formulation to 24 volunteers. Inset shows the initial portion of the profile on a linear–linear scale.

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**Chemical Structure**

![Chemical Structure](image)

**Chemical Formula:**

\[C_{60}H_{111}N_{11}O_{12}\]  Mol. Wt. 1202.63

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**Before**

Dilution

**After**

Dilution
Current Success Stories

*Kaletra® - Amorphous Dispersion for Improve Delivery*

**Kaletra Soft Gelatin Capsule**
- Dose per unit: 133 mg lopinavir/33 mg ritonavir
- Dose administration: t.i.d. with food
- Refrigerated storage required

**Kaletra Tablet**
- Dose per unit: 200 mg lopinavir/50 mg ritonavir
- Dose administration: b.i.d. independent of food
- Store at ambient conditions

*Rosenberg et al. Patent # WO 2006/091529 A2*
Current Success Stories

Zelboraf® - Molecule to Medicine with Novel Technology

- Poor Solubility >>>>> Poor Bioavailability
- Polymorphic Transformation (metastable Form I to stable Form II) >>>>> Clinical Supply Stock-out Situation
- High Dose >>>>> Patient Dosing Convenience
Current Success Stories
Zelboraf® - Making a Difference in Therapy

- Development of an amorphous formulation enabled a molecule which could otherwise not be delivered → Life saving benefit to patients in need
- Successful implementation of new technology led to commercial product

Bioavailability Comparison

Treatment Results in Tumor Regression
Oral Formulations Approaches for Poorly Water Soluble Compounds (BCS 2/4 compounds)

<table>
<thead>
<tr>
<th>Conventional</th>
<th>No-Convention: Risk and complexity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Salts</td>
<td>SEDDS/SMEDDS</td>
</tr>
<tr>
<td>Pro-drug</td>
<td>Nanoparticles</td>
</tr>
<tr>
<td></td>
<td>Polymeric micelles</td>
</tr>
<tr>
<td></td>
<td>Dendrimers</td>
</tr>
<tr>
<td>Particle size reduction</td>
<td>Complexes Co-crystals</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Need for amorphous formulation has significantly increased
Chemical approach using reversible derivatives that is pharmacologically inert

Successfully applied to a number of commercially marketed products

Advantages
• NCE, Patentable
• Enhanced biopharmaceutical performance

Opportunities
• Reducing development cost
• Site targeted prodrug design
• Expanding chemistries

Prodrugs represent a Chemical/Biochemical approach to the Optimization of Drug Delivery

VX-175/GW 908
(A Phosphate Prodrug of Amprenavir)

7 fold increase in solubility
Technologies to Improve Solubility

PARTICLE SIZE REDUCTION

Advantages
- **Improve exposure** – reduce dose
- **Faster onset of action** – improve efficacy
- **Minimize variability** – improve efficacy and decrease toxicity
- **Reduce/eliminate food effect** – improve convenience and compliance

Opportunities
- **Need for more advanced MFG technologies** – Imprinting, Templating, etc…
- **Expansion of nanotechnology into drug-device hybrid products** – MEMs technology
- **Lower cost of goods for manufacturing** – Current technologies are expensive, proprietary and time consuming
Technologies to Improve Solubility

LIPID FORMULATIONS

Formulation Concept

- SEDDS
- Coarse emulsion
- Water
- Micelle (L1 phase)
- a/w microemulsion
- bicontinuous microemulsion

Biological Interaction

- Drug-lipid droplets
- Digestion and emulsification
- Partitioning
- Bile Salt-phospholipid mixed micelles

Oral Bioavailability Enhancement

Advantages

- Reduced food effect
- Permeability enhancement
- Liquid nature provides for ease of scale-up

Opportunities

- Expansion of materials to support formulation development
- New technologies to improve manufacturability
Technologies to Improve Solubility

**CYCLODEXTRINS**

Cyclodextrins

Oligosaccharides (6 or more glucopyranose units)

Forms inclusion complexes with drugs
  - Steric
  - Thermodynamic interactions

**Advantages**
- Enhanced drug delivery through biological membranes
- Increased stability

**Opportunities**
- Improve stability of cyclodextrin in the intestinal environment

Technologies to Improve Solubility

**POLYMERIC MICELLES**

Self-assembling amphiphilic polymer
(i.e. poly(ethylene oxide)-b-poly(L-amino acid))
(PEO-\textit{b}-PLAA)) forms micelles (< 100 nm)

- Provides sites for attachment of drugs
- Better kinetic and thermodynamic stability than surfactant based micelles

**Advantages**
- Stays unrecognized during blood circulations
- Extended circulation time
- Lower toxicity

**Opportunities**
- Loading efficiency

Technologies to Improve Solubility

AMORPHOUS TECHNOLOGIES

Advantages

• Supports solid dosage form
• Continuous manufacturing
• Potential for greater exposure than other technologies

Opportunities

• Develop predictive tools for dispersions
• New materials to improve exposure and drug loading
• New technologies to improve manufacturing

AMORPHOUS MANUFACTURING

Spray Drying (SDD)
- Solvent evaporation
- Low boiling solvent

Microprecipitation (MBP)
- Solvent/antisolvent
- Enables high BP solvent

Hot Melt Extrusion (HME)
- Temp. and shear
- Non-solvent

Fluid-bed layering (FBL)
- Drug/polymer layering
- Solvent evaporation
- Low boiling solvent

SOLUBILITY ADVANTAGE

Achieving Supersaturation
Particle Size Reduction

Steric Hindrance
Interfacial Energy Modification
Solubilizers

THERMODYNAMIC PROPERTIES

Volume, Enthalpy

Supercritical liquid

Liquid

Glass

Crystal

Temperature

Concentration (mg/L)

0 10 20 30 40 50 60

0 5 10 15

Time (min)

Tg

Tm
Examples of Commercial Products Using Amorphous API or ASD

<table>
<thead>
<tr>
<th>Product</th>
<th>Form</th>
<th>Mol.Wt</th>
<th>Tm</th>
<th>Tg</th>
<th>Tm/Tg (C/C)</th>
<th>Tm/Tg (K/K)</th>
<th>Log P</th>
<th>Marketed Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zafiralukast</td>
<td>Amo. API</td>
<td>575.7</td>
<td>139</td>
<td>98</td>
<td>1.4</td>
<td>1.1</td>
<td>4.8</td>
<td>Accolate (GSK)</td>
</tr>
<tr>
<td>Rosuvastatin Ca</td>
<td>Amo. API</td>
<td>481.5</td>
<td>135</td>
<td>102</td>
<td>1.3</td>
<td>1.1</td>
<td>1.5</td>
<td>Crestor (AZ)</td>
</tr>
<tr>
<td>Quniapril HCl</td>
<td>Amo. API</td>
<td>474.9</td>
<td>125</td>
<td>91</td>
<td>1.4</td>
<td>1.1</td>
<td>0.9</td>
<td>Accupril (Pfizer)</td>
</tr>
<tr>
<td>Nelfinavir Mes.</td>
<td>Amo. API</td>
<td>663.9</td>
<td>133</td>
<td>105</td>
<td>1.3</td>
<td>1.1</td>
<td>4.1</td>
<td>Viracept (Pfizer)</td>
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<tr>
<td>Itraconazole</td>
<td>ASD</td>
<td>705.6</td>
<td>166</td>
<td>59</td>
<td>2.8</td>
<td>1.3</td>
<td>5.6</td>
<td>Sporanox (Jansen)</td>
</tr>
<tr>
<td>Ritonavir</td>
<td>ASD</td>
<td>720.3</td>
<td>123</td>
<td>87</td>
<td>1.4</td>
<td>1.1</td>
<td>4.9</td>
<td>Norvir (Abbott)</td>
</tr>
<tr>
<td>Lopinavir</td>
<td>ASD</td>
<td>628.8</td>
<td>125</td>
<td>101</td>
<td>1.2</td>
<td>1.1</td>
<td>~4.3</td>
<td>Kaletra* (Abbott)</td>
</tr>
<tr>
<td>Telaprevir</td>
<td>ASD</td>
<td>679.9</td>
<td>246</td>
<td>105</td>
<td>2.3</td>
<td>1.4</td>
<td>3.5</td>
<td>Incivek (Vertex)</td>
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<tr>
<td>Vemurafenib</td>
<td>ASD</td>
<td>489.9</td>
<td>270</td>
<td>109</td>
<td>2.5</td>
<td>1.4</td>
<td>3.8</td>
<td>Zelboraf (Roche)</td>
</tr>
</tbody>
</table>

- Pure amorphous API poses much higher risk compared to ASD
- Development of stabilized ASD is preferred
- Successful commercialization of ASDs has been achieved with multiple technologies
Challenges for Predicting Suitability & Stability of Amorphous Dispersions

- Heating & Cooling method has an issue of decomposition of the compound with high melting point
- The compound of "easy amorphous" can be categorized into non-crystallizing compounds and has low Tm/Tg ratio
- Even if a compound has low Tm/Tg ratio and categorized as "easy amorphous", the compound can still be difficult to make amorphous.
Dissolution Methods and Challenges

- High energy systems prone to crystallize during dissolution
- Crystallization kinetics depend on Temperature, Sink Condition and Media Composition
- Drug may be associated with polymer (free drug vs. bound drug)
- Higher supersaturation generally causes faster precipitation (lower recovery)

Judicious selection of dissolution condition is critical for “meaningful” interpretation of data.
Amorphous Processing Technology Selection Guide

<table>
<thead>
<tr>
<th>Melting Point</th>
<th>Microprecipitation</th>
<th>Spray Drying</th>
</tr>
</thead>
<tbody>
<tr>
<td>HME</td>
<td>Solubility in volatile solvents</td>
<td></td>
</tr>
<tr>
<td>Spray drying</td>
<td>HME</td>
<td></td>
</tr>
</tbody>
</table>

Compounds with melting point < 200°C could be suitable for HME and compounds with solubility > 50 mg/mL in low boiling point volatile solvent are suitable for SD.
## Pros & Cons of Amorphous Technologies

<table>
<thead>
<tr>
<th>Technology</th>
<th>Pros</th>
<th>Cons</th>
</tr>
</thead>
</table>
| Melt Extrusion      | Non-solvent based  
Short exposure to high temperature  
Modular design provides flexibility  
Extrudate density helps improve stability  
Continuous process  
Established scale-up and commercial feasibility | Thermal degradation  
Limited application for high T$_m$ compounds  
Dissolution (erosion)  
Reduced compactability |
| Spray Drying        | Rapid removal of solvent  
Established scale-up and commercial feasibility  
Processing occurs below T$_g$  
Applicable for low boiling point, low toxicity solvents (i.e. ethanol, acetone) | Requires adequate solubility in volatile solvent  
Residual solvent levels must be tested  
Phase separation may occur based on solubilities  
Low bulk density requires densification |
| Microprecipitation  | Useful for compounds not amenable to HME or SD  
Provides high degree of super-saturation (ionic interaction)  
Modulated plasma profile due to enteric polymer  
Semi-continuous processing | Require ionic polymers  
Not suitable for weakly basic drugs  
Solvent extraction may require multiple washings  
Downstream processing required  
Scale-up challenges exist |

It is important to select the right process for the molecule, not force a process onto the compound! If necessary consider other novel technologies (i.e. mesoporous silica, KinetiSol)
Opportunities for New Technologies

Case Study with Mesoporous Silica

• Mesoporous silica can improve dissolution rates and exposure of poorly soluble compounds

Mellaerts et al., EJPB. 69 2008, p. 223
Opportunities for New Technologies

Case Study with KinetiSol

Melt Extrusion

<table>
<thead>
<tr>
<th>Polymer</th>
<th>Particle size</th>
<th>Temperature (°C)</th>
<th>Screw speed (rpm)</th>
<th>Recirculation time (min)</th>
<th>Recovery (%)</th>
<th>Impurities (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eudragit® RS100-55</td>
<td>Unmilled</td>
<td>140</td>
<td>300</td>
<td>2</td>
<td>22.7±0.5</td>
<td>55.9</td>
</tr>
<tr>
<td>Eudragit® RS100-55</td>
<td>Micronized</td>
<td>140</td>
<td>300</td>
<td>2</td>
<td>69.1±0.5</td>
<td>17.5</td>
</tr>
<tr>
<td>HPMCAS</td>
<td>Unmilled</td>
<td>170</td>
<td>300</td>
<td>0</td>
<td>70.9±0.3</td>
<td>10.2</td>
</tr>
<tr>
<td>HPMCAS</td>
<td>Micronized</td>
<td>170</td>
<td>300</td>
<td>0</td>
<td>76.4±0.4</td>
<td>8.9</td>
</tr>
</tbody>
</table>

KinetiSol

<table>
<thead>
<tr>
<th>Polymer</th>
<th>Particle size</th>
<th>Speed (rpm)</th>
<th>Temp. (°C)</th>
<th>Recovery (%)</th>
<th>Impurities (%)</th>
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</thead>
<tbody>
<tr>
<td>Eudragit® RS100-55</td>
<td>Unmilled</td>
<td>1,450</td>
<td>100</td>
<td>70.9±0.3</td>
<td>12.9</td>
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<tr>
<td>HPMCAS</td>
<td>Unmilled</td>
<td>2,400</td>
<td>112</td>
<td>96.4±1.2</td>
<td>1.6</td>
</tr>
</tbody>
</table>

- Application of new technologies offers the possibility to significantly expand manufacturing window
Future Directions

**TODAY**

- Many industrial pipelines have solubility limitations
- Limited number of approved excipients for solubility enhancement
- Simple models and descriptors predict stability and performance of advanced systems
- Batch manufacturing processes with a limited portfolio of techniques to prepare advanced systems

**TOMORROW**

- Chemistry of compounds becomes highly engineered to reduce solubility liabilities
- Pharma companies and excipient manufacturers work jointly to develop excipients with unique advantages
- In silico methods advance to provide computer aided design and a priori prediction
- Continuous manufacturing and new technologies provide advantages to poorly soluble compounds
Summary Remarks

- Even today, poorly soluble compounds present major development challenges that may limit or even prevent a life saving medication from reaching the market
  - Drives substantial investments in new technologies and products

- Limitations of materials and technologies present unique opportunities for partnerships and collaborations to develop these areas
  - Will generate new models for conducting business and developing therapies

- True innovation allows a molecule to become a medicine
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Questions