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Contents

1. **Prodrugs**: Definition and impact in Pharma

2. **Prodrug challenges to be met**:
   - Formulation, *in vivo* stability & bioconversion
   - The regulatory pathway

3. **Example prodrug handles and subsequent functional prodrugs**

4. **A prodrug program Research Operating Plan (ROP)**
   - Prioritizing activities on identifying and characterizing prodrug leads

5. **Case Study: Permeability Enhancement Via a Prodrug Strategy**
   - An ambitious example of a prodrug strategy to increase colonic absorption to enable a CR formulation for QD dosing
What is a prodrug?

A bioreversible derivative of an active drug compound:
- Undergoes \textit{in vivo} enzymatic or chemical transformation to release active parent drug compound

Today: Context of absorption, \textit{not} targeting

Audience Survey Question

Which can NOT be influenced by a Prodrug?
- Cell permeability
- Administration route
- Half life
- Intellectual property
- None of the above
What Benefits Can a Prodrug Provide?

• Improved properties related to ADME
  – ↑ aqueous solubility
  – ↑ permeability
  – ↑ chemical stability
  – ↓ pre-systemic metabolism

• New/ improved delivery options
  – Oral ⇒ Topical

• Life cycle management

• Targeted delivery (another day’s topic)

• Additional intellectual property (IP)

When to Engage a Prodrug Strategy?

The Discovery Debate on a candidate with sub-optimal physchem properties:

• Fix it now via a prodrug? ⇒ More complex synthesis, tox, regulatory pathway
• Fix it later via an enabled formulation? ⇒ Longer/more costly & complex dosage form development

Real life observation:

• Insoluble, highly crystalline candidate was advanced as a low drug-load amo dispersion ⇒ led to nightmarish, dose limited, high-cost formulation
• Later on, a soluble prodrug was identified…probably too late!

The prodrug conversation must be had EARLY by the Lead Ops team!
Prodrugs:
Recently Overheard in Discovery Hallways

Comment: Let's fix our bioavailability problems with a prodrug!

Responses:

• “No; I love my parent compound and you formulators can fix it through drug delivery.”
• “No, prodrugs are the last resort for poor medicinal chemistry efforts.”
• “Prodrugs are for losers.”

Audience Survey Question

What percentage of the Top 100 Blockbuster Drugs are actually Prodrugs?

• Less than Two percent
• About Five percent
• About Fifteen percent
• About Twenty percent
Prodrugs: More Common Than You Think!

The Pharma Industry:

- 15% of the 100 blockbuster drugs are prodrugs!

Some Blockbuster Prodrugs:

- Omeprazole, Prilosec®, proton pump inhibitor: permeation
- Acyclovir, Zovirax®, anti-viral: liver targeting
- Enalapril maleate, Vasotec®, ACE inhibitor: permeation
- Simvastatin, Zocor®, HMG-CoA reductase inhibitors: liver targeting

Clas et al., 2013; Landis, 2013.

Aprepitant (Emend®) Example

A poorly soluble compound: Two Enabling methods for two administrations routes

Oral Dosage Form: Nanoparticles

IV Solution: Phosphate Prodrug
Prodrugs Do Have Potential Challenges

**Poor formulation stability**
- Converts to parent

**Poor stability in stomach**
- Converts to parent

**Prodrug too stable in vivo**
- No bioconversion to parent

All this must be interrogated

Potential Assays to Probe Bioconversion

1. **In vitro stability & solubility**
   - Biological Media: Simulated GI fluids (SGF, FaSSIF) with and without digestive enzymes
   - Buffers (formulation & serum conversion prediction)
2. **In vitro permeability assays** (Caco-2, LLC-PK1…)
3. **In vitro** stability in hepatocytes and plasma
4. **In vivo** PK and bioconversion
   - Look for circulating prodrug and parent in plasma
   - Rat and/or dog most common preclinical species
   - Beware of species differences (i.e. high metabolism in rat; Esterase activity is species dependent)
What are the toxicology and regulatory considerations for Prodrugs?

- Circulating prodrug levels
- Bioconversion
- Regulatory input
- All of the above
- None of the above

Prodrugs’ Toxicology & Regulatory Considerations

Prodrugs still require thorough safety evaluation

Circulating prodrug levels

Bioconversion

- Species differences
- By-product characterization (i.e. formaldehyde)

Regulatory input

Prodrug Development to FIH is typically same as any new chemical entity even when parent molecule is already approved

TOX STUDIES MUST BE REPEATED: CASE FOR CONSIDERING EARLY IN THE DISCOVERY PHASE!
**Common “Prodruggable” Handles and Subsequent Functional Prodrugs**

<table>
<thead>
<tr>
<th>Parent Handle</th>
<th>Prodrug Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcohols</td>
<td>Esters (incl. amino acids (AAs)); Phosphates/Phosphonates*</td>
</tr>
<tr>
<td>Amines</td>
<td>Amides, Phosphates/Phosphonates Sulfenamides*</td>
</tr>
<tr>
<td>Carboxylic Acids</td>
<td>Esters (incl. AAs)</td>
</tr>
<tr>
<td>Phenols</td>
<td>Esters (incl. AAs); Phosphates/Phosphonates</td>
</tr>
<tr>
<td>Thiols</td>
<td>Thioethers/esters</td>
</tr>
</tbody>
</table>

- **Solubility**: ionization/polarity, lipophilicity (log D)
- **Permeability**: The opposite of above

* Phosphate

![Chemical structures](image)

*Sulfenamide

*Oxymethylphosphate

Stella, *Prodrugs: Challenges & Rewards, 2007*

**Example ROP: A Prodrug Strategy for Enhancing Permeability**

- **Promoieties** selected to increase lipophilicity
- **in vitro** screening for prodrug viability:
  - Solubility, log P
  - Chem Stability (GI, formulation)
  - Cell permeability
- **In vivo** PK and bioconversion studies in preclinical species

*In silico permeability modeling*

- Solubility/Stability/log P
- **Cell Permeability**
- **In vivo PK evaluation**
- **Data assimilation**
Case Study:
Prodrug to Enable a CR Formulation

- **Compound A**: Short half-life (1.5h) required BID dosing ⇒ QD preferred
  - Low permeability although good intestinal absorption observed
- **Controlled release formulation for once daily (QD) dosing?**
  - NO: Poor permeability led to poor colonic absorption, which makes controlled release (CR) formulations impossible
- **Compound A contained an ionizable phenol** that contributed to poor permeability (pKa 6.7)
  - Also a prodrug handle...

![](image1.png)

Prodrug Strategy to Enable Colonic Absorption and a CR Formulation

Can a prodrug that masks phenol ionization increase permeability and colonic absorption to enable a CR QD formulation?

![](image2.png)

A modified release dosage form to bypass the intestine (good absorption there) also would be required…(colonic delivery…another day’s topic)

Ref. Sophie-Dorothee Clas, Becky Nofsinger, Abbas Walji
Case Study: Colonic Prodrug ROP

- Modelled >80 prodrug structures for calculated Papp (cLog P)\(^1\)
- Selected 20 for synthesis

Candidate Selection Criteria
1. \(P_{app} \geq 10\times \text{Parent?}\)
2. Bioconversion \(\geq 90\% \text{ in 1h?}\)
3. Formulation stability \(\geq 3\text{h?}\)
4. >30% colonic absorption?

\(^{1}\text{Accelrys Cerius2 Software}\)
\(^{2}\text{Simulated gastric and fasted intestinal fluids}\)
\(^{3}\text{Cell line: LLC-PK1}\)

Dog Colonic Absorption Study:
Retrograde Catheter Dosing in Beagle dogs

- Experiment is based on % relative absorption: Colonic AUC/Oral AUC
- Predictive of human colonic absorption

Administer catheter here

Case Study: Lead Carbonate-ester Prodrug Structures

Ph-OH = Phenol

Ph-OH →

[Chemical structures A to F]

Walji, ChemMedChem 2015, 10, 245 – 252

Carbonate Ester Physchem Properties

<table>
<thead>
<tr>
<th>Compound</th>
<th>cLogP¹</th>
<th>Solubility in SGF² (mg/mL) 1hr</th>
<th>Solubility FaSSIF² (mg/mL) 1hr</th>
<th>Stability in SGF² (1hr) %Claim</th>
<th>Stability in FaSSIF (5hr) %Claim</th>
<th>Hepatocyte parent conversion &lt;1hr?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parent</td>
<td>-0.7</td>
<td>0.01</td>
<td>0.50</td>
<td>98.36%</td>
<td>99.40%</td>
<td>n/a</td>
</tr>
<tr>
<td>Prodrug A</td>
<td>0.9</td>
<td>0.37</td>
<td>0.33</td>
<td>93.80%</td>
<td>90.97%</td>
<td>Yes</td>
</tr>
<tr>
<td>Prodrug B</td>
<td>1.3</td>
<td>0.02</td>
<td>0.03</td>
<td>100.02%</td>
<td>99.92%</td>
<td>Yes</td>
</tr>
<tr>
<td>Prodrug C</td>
<td>1.5</td>
<td>0.04</td>
<td>0.25</td>
<td>99.32%</td>
<td>98.27%</td>
<td>Yes</td>
</tr>
<tr>
<td>Prodrug D</td>
<td>1.3</td>
<td>0.06</td>
<td>0.06</td>
<td>100.14%</td>
<td>101.61%</td>
<td>Yes</td>
</tr>
<tr>
<td>Prodrug E</td>
<td>0.4</td>
<td>6.6</td>
<td>0.60</td>
<td>95.50%</td>
<td>96.27%</td>
<td>Yes</td>
</tr>
<tr>
<td>Prodrug F</td>
<td>2.2</td>
<td>0.02</td>
<td>0.04</td>
<td>91.32%</td>
<td>98.45%</td>
<td>Yes</td>
</tr>
</tbody>
</table>

¹ Apparent octanol/water partition coefficient (cLogP) calculated using Accelrys Cerius2 Software
Carboante Ester cLogP and Permeability

<table>
<thead>
<tr>
<th>Compound</th>
<th>cLogP</th>
<th>LLC-PK1 Papp (*10^-6 cm/sec)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parent</td>
<td>-0.7</td>
<td>11.6</td>
</tr>
<tr>
<td>Prodrug A</td>
<td>0.9</td>
<td>5.8</td>
</tr>
<tr>
<td>Prodrug B</td>
<td>1.3</td>
<td>8.9</td>
</tr>
<tr>
<td>Prodrug C</td>
<td>1.5</td>
<td>11.9</td>
</tr>
<tr>
<td>Prodrug D</td>
<td>1.3</td>
<td>11.9</td>
</tr>
<tr>
<td>Prodrug E</td>
<td>0.4</td>
<td>1.7</td>
</tr>
<tr>
<td>Prodrug F</td>
<td>2.2</td>
<td>15.4</td>
</tr>
</tbody>
</table>

cLog P does NOT correlate well with cell permeability…?

Colonic Dog Study Results

<table>
<thead>
<tr>
<th>Compound Dosed (solution vehicle)</th>
<th>Dose (mpk)</th>
<th>Dosing Route</th>
<th>nAUC0-24hr (µM*h/ mpk)</th>
<th>Dog Colonic Absorption (vs. oral, n = 3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parent (3% Tween)</td>
<td>4</td>
<td>Oral</td>
<td>2.92 ± 0.48</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Colonic</td>
<td>0.30 ± 0.26</td>
<td>9%</td>
</tr>
<tr>
<td>Prodrug A (3% Tween)</td>
<td>4</td>
<td>Oral</td>
<td>1.91 ± 0.12</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Colonic</td>
<td>0.76 ± 0.21</td>
<td>40%</td>
</tr>
<tr>
<td>Prodrug B (10% Tween)</td>
<td>1</td>
<td>Oral</td>
<td>0.94 ± 0.05</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Colonic</td>
<td>0.40 ± 0.13</td>
<td>43%</td>
</tr>
<tr>
<td>Prodrug C (10% Tween)</td>
<td>1</td>
<td>Oral</td>
<td>0.77 ± 0.13</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Colonic</td>
<td>0.24 ± 0.04</td>
<td>31%</td>
</tr>
<tr>
<td>Prodrug D (30% Captisol®)</td>
<td>4</td>
<td>Oral</td>
<td>2.4 ± 0.14</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Colonic</td>
<td>0.72 ± 0.07</td>
<td>30%</td>
</tr>
<tr>
<td>Prodrug E (10% Tween)</td>
<td>0.7</td>
<td>Oral</td>
<td>4.35 ± 1.3</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Colonic</td>
<td>0.24 ± 0.15</td>
<td>5%</td>
</tr>
<tr>
<td>Prodrug F (10% Tween)</td>
<td>1</td>
<td>Oral</td>
<td>0.75 ± 0.02</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Colonic</td>
<td>0.07 ± 0.13</td>
<td>10%</td>
</tr>
</tbody>
</table>
Conclusions

• Prodrugs are prevalent in the industry and an effective means of improving physchem properties
• Need to consider early in Discovery phase before it's too late
• Need to be aware of specific tox and regulatory challenges
• Case study: Demonstrated that a lipophilic prodrug can increase colonic absorption
  • Of note: The cLog P and LLC-PK1 permeability did not correlate well with subsequent colonic absorption
  • Interplay between several physchem attributes and oral bioavailability
  • Next comes a formulation challenge to deliver prodrug to the colon….another day’s topic

References

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• Pham-The, H.; Garrigues, T.; Bermejo, M.; Gonzalez-Alvarez, I.; Monteagudo, M.C.; Cabrera-Perez, M.A. 2013 “Provisional Classification and in Silico Study of Biopharmaceutical System Based on Caco-2 Cell Permeability and Dose Number” Mol. Pharmaceutics. 10, 2445-2461.

General Prodrug References

Additional References

**Intestinal pH**
- Davies, B; Morris, T. 1993 "Physiological Parameters in Laboratory Animals and Humans" Pharm. Res. 10, 1093-1095.

**Colonic Delivery**

**Dog colonic model**

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