Improvement of oral bioavailability using prodrugs

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Prodrug concept

Rautio et al. Prodrugs - design and clinical applications.
How to make prodrugs?

Selection of the promoiety:

- Which functional groups are amenable to derivatization?
- Chemical modifications made must be reversible, and allow the prodrug to be converted back into the parent drug by an in vivo chemical and/or enzymatic reaction.
- The promoiety should be safe and rapidly excreted from the body.
- The absorption, distribution, metabolism, excretion (ADME) properties of parent drug and prodrug require a comprehensive understanding.
- Possible degradation byproducts can affect both chemical and physical stability that lead to the formation of new degradation products.
Prodrug approaches for improved oral bioavailability

1) Increased aqueous solubility
2) Increased lipophilicity
3) Transporter-mediated drug delivery
Water-soluble prodrug for oral delivery

- There are surprisingly few examples of commercial successes where prodrugs have been used to improve the oral delivery of sparingly water-soluble drugs!

- Applicable especially to drugs that have:
  - low solubility but high permeability (in \textit{in vitro} assays, e.g., Caco-2)
  - high dose
  - low or moderate hepatic clearance in rats or other preclinical species
  - high mp and crystallinity leading to poor water and lipid solubility ("brick dust" molecules)
Addition of non-ionizable polar functionality

- Non-ionizable, polar sulfoxide functionality
- ~100-times more water-soluble (3.3 mg/ml vs. 0.03 µg/ml) at pH 7.4
- log D (pH 7.4) = 1.52
Addition of ionizable phosphate functionality

Pros
- Chemically stable
- Synthesis usually straightforward
- Increased solubility several orders of magnitude
- Rapidly cleaved by endogenous alkaline phosphatases

Cons
- Parent must be permeable once cleaved
- Too rapid cleavage of a very insoluble parent can result in precipitation and poor re-dissolution

Successful phosphate prodrugs for oral delivery

Amprenavir
- For the treatment of HIV infection
- Aq. sol. = 41 µg/ml
- Good bioavailability (≈ 80%)
- High percentage of excipients due to low solubility requiring 8 capsules two times daily
- Marketed since 1999

Fosamprenavir
- Aq. sol. = 0.3 mg/ml
- Biological transformation by brush border gut phosphatase
- Equal bioavailability with amprenavir
- Identical preclinical safety profile
- Due to better solubility requires only 3 tablets two times daily
- Patent protection continues longer
Successful phosphate prodrugs for oral delivery

**Estramustine phosphate (Emcyt®)**
Marketed both as injectable and oral formulations for the treatment of prostate carcinoma since the mid 1970s.

**Prednisolone phosphate (Pediapred®)**
Enabled the development of a liquid formulation, and thus, improved children’s’ compliance to prednisolone treatment.

**Fludarabine phosphate (Fludara®)**
Until recently, fludarabine phosphate was marketed only for parenteral use. Based on a modest advantage over the parent drug, development of an oral prodrug of fludaribine may have only been a consequence of prior existence of a commercial parenteral prodrug.
Unsuccessful phosphate prodrugs for oral delivery

Entacapone
- Oral bioavailability ~25-46 %
- Aq. sol. = 17 mg/ml (pH 1.2); 1.75 mg/ml (pH 7.4)
- Poor dissolution rate in the pH range of stomach and upper small intestine => low and variable bioavailability ???

Entacapone phosphate
- Aq. sol. ≥ 30 mg/ml at pH 7.4
- Chemically stable
- Rapidly cleaved by alkaline phosphatases
- Bioavailability of prodrug less than that of entacapone solution (pH 7.4)
- Low permeability and/or high systemic clearance main barriers ??
Lipophilic prodrugs for oral delivery

“Case Tamiflu®”

- Zanamivir (Relenza®, GSK)
- Neuraminidase inhibitor for the treatment of Influenzavirus A and B
- Suffers from poor oral bioavailability (2 %)
- Available commercially as an inhaled product (BA about 15 %)
- Zanamivir was the first neuraminidase inhibitor to the market in 1999 but it had only a few months lead over the second entrant, oseltamivir (Tamiflu®), with an oral tablet formulation
Lipophilic prodrugs for oral delivery

Oseltamivir carboxylate
- Influenza A and B
- Exists as a poorly lipophilic zwitterionic amino acid
- Oral bioavailability less than 5% in humans

Oseltamivir ethyl ester
- Oral bioavailability in humans 80%
- Bioconverted by carboxylesterases
- By the end of flu season in 1999 Tamiflu was outselling zanamivir 3:1 - dominance has since increased
# Problems associated with some ester prodrugs

<table>
<thead>
<tr>
<th>Animal species</th>
<th>Compound</th>
<th>Oseltamivir carboxylate % bioavailability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mouse</td>
<td>Prodrug</td>
<td>30</td>
</tr>
<tr>
<td>Rat</td>
<td>Prodrug</td>
<td>35</td>
</tr>
<tr>
<td>Dog</td>
<td>Prodrug</td>
<td>73</td>
</tr>
<tr>
<td>Human</td>
<td>Oseltamivir carboxylate</td>
<td>4.3</td>
</tr>
<tr>
<td>Human</td>
<td>Prodrug</td>
<td>80</td>
</tr>
</tbody>
</table>
Problems associated with some ester prodrugs

Apical lumen

Enterocytes

Basolateral blood

PD → D-

PD → D-

PD → D-
Possible solution for premature bioconversion?

**Sulfenamide prodrug approach**
- Acidic and basic amines
- Prodrug is chemically stable
- Bioconversion in seconds *in vivo* after po absorption
- More lipophilic (log D -3.4 vs. 0.5 at pH 7.4)
- Bioavailability increased by 20% in rats (from 40% to 60%)

Lipophilic prodrugs for oral delivery

**Tenofovir**
- Acyclic nucleoside phosphonate
- Tenofovir diphosphate is a potent and selective inhibitor of viral reverse transcriptase and effectively blocks viral replication
- Exist as a dianionic at physiological pH
- The log P is less than -3 at pH 6.5
- Demonstrates low and erratic oral bioavailability in animal studies (mice 1.9%, rat 6.0%, monkey 2.7, dog 17.7)

Adefovir dipivoxil (Hepsera®)
### Lipophilic prodrugs for oral delivery

<table>
<thead>
<tr>
<th>Cmpd</th>
<th>Log P pH 6.5</th>
<th>$t_{1/2}$ (hr) pH 7.4</th>
<th>$t_{1/2}$ (min) dog intestinal homog.</th>
<th>$t_{1/2}$ (min) dog plasma</th>
<th>$t_{1/2}$ (min) dog liver homog.</th>
<th>% F in dogs</th>
</tr>
</thead>
<tbody>
<tr>
<td>![Chemical Structure]</td>
<td>1.3</td>
<td>9.2</td>
<td>52.6</td>
<td>20.5</td>
<td>&lt;5</td>
<td>30.1</td>
</tr>
<tr>
<td>![Chemical Structure]</td>
<td>2.1</td>
<td>14</td>
<td>10.4</td>
<td>35.5</td>
<td>&lt;5</td>
<td>37.8</td>
</tr>
<tr>
<td>![Chemical Structure]</td>
<td>0.6</td>
<td>7.0</td>
<td>23.3</td>
<td>16.6</td>
<td>&lt;5</td>
<td>24.5</td>
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<tr>
<td>![Chemical Structure]</td>
<td>2.7</td>
<td>6.0</td>
<td>&lt;5</td>
<td>&lt;5</td>
<td>&lt;5</td>
<td>18.0</td>
</tr>
<tr>
<td>![Chemical Structure]</td>
<td>2.0</td>
<td>9.0</td>
<td>15</td>
<td>&lt;5</td>
<td>&lt;5</td>
<td>20.8</td>
</tr>
<tr>
<td>![Chemical Structure]</td>
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<td>0.4</td>
<td>26.6</td>
<td>21.2</td>
<td>14.9</td>
<td>30.7</td>
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<tr>
<td>![Chemical Structure]</td>
<td>&gt;3.0</td>
<td>6.0</td>
<td>&lt;5</td>
<td>&lt;5</td>
<td>&lt;5</td>
<td>16.0</td>
</tr>
<tr>
<td>![Chemical Structure]</td>
<td>&gt;3.9</td>
<td>8.0</td>
<td>30</td>
<td>15</td>
<td>&lt;5</td>
<td>28.8</td>
</tr>
</tbody>
</table>
Lipophilic prodrugs for oral delivery

Conversion of oxymethyloxycarbonyl linker

\[
\text{ROH} \rightarrow \text{Esterases} \rightarrow \text{Spontaneous} \rightarrow \text{Spontaneous}
\]

\[
\text{CO}_2 \rightarrow \text{Spontaneous}
\]

\[
\text{CH}_2\text{O} \rightarrow \text{Spontaneous}
\]
Successful lipophilic prodrugs for oral delivery

**Dabigatran etexilate (Pradaxa®)**
The oral anticoagulant that has bioavailability of 3-7% as such but can be increased up to 75% by formulation.

**Olmesartan medoxomil (Benicar®)**
The oral bioavailability in humans is 26%. Completely bioactivated during absorption (designed for paraoxonases).

**Enalapril (Vasotec®)**
The oral bioavailability of enalapril in humans is 36-44%.

**Famciclovir (Famvir®)**
The oral bioavailability of 4% for penciclovir increased to 75% for famciclovir.
Transporter-mediated prodrugs for oral delivery - PePT1
Transporter-mediated prodrugs for oral delivery - PePT1

**Aciclovir** (Zovirax® etc.)
- Inhibitor of the replication of herpesvirus
- Poor and variable oral bioavailability (15-21%)

**Valaciclovir** (Valtrex® or Zelitrex®)
- Improves oral bioavailability by 3-5 - fold via PePT1
- Several amino acid prodrugs undergoing clinical trials!
Many antivirals are prodrugs as such!

Valacyclovir

Hydroxylation by esterases

Acyclovir

Monophosphorylation by viral thymidine kinase

Therapeutically active triphosphorylated species

Phosphorylation by cellular kinase
Transporter-mediated prodrugs for oral delivery - Monocarboxylate transporter (MCT)

**Gabapentine**
- Anticonvulsant (e.g., epilepsy)
- Saturable absorption (LAT-substrate)
- High inter-patient variability
- Lack of dose proportionality
- Short half-life (5-7 h)
- 3-4 doses a day

**Gabapentin enacarbil**
- Substrate of MCT-1 (also SMVT)
- Improved bioavailability (from 25% after a similar gabapentine dose to 84% in monkeys)
- No saturation observed with therapeutic doses
- Releases rapidly gabapentine in intestinal and liver tissues
- Showed higher levels of gabapentine in the blood for a longer period of time in clinical trials (Phase 2 completed)

SMVT = sodium-dependent multivitamin transporter
Prodrug prevalence

- Currently about 10% of all world-wide approved drugs are prodrugs.


- Prodrug prevalence is 15.4% among the 100 best selling small molecular weight drugs in 2008 (14/91).

Stella: J Pharm Sci 99(12): 4755-4765, 2010
<table>
<thead>
<tr>
<th>Prodrug name (therapeutic area)</th>
<th>Functional group</th>
<th>Prodrug strategy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Esomeprazole, Lansoprazole, Pantoprazole, Rabeprazole (proton pump inhibitors)</td>
<td>Formation of active sulphenamide form</td>
<td>Bioprecursor prodrugs that are converted into their respective active sulphenamide forms site-selectively in acidic conditions of stomach</td>
</tr>
<tr>
<td>Clopidogrel (antiplatelet)</td>
<td>Formation of the active thiol</td>
<td>Bioprecursor prodrug that selectively inhibits platelet aggregation</td>
</tr>
<tr>
<td>Valacyclovir (antiviral)</td>
<td>L-Valyl ester of acyclovir</td>
<td>Bioconversion by valacyclovir hydrolase (valacyclovirase). Transported predominantly by hPEPT1. Oral bioavailability improved from 12-20% (acyclovir) to 54% (valacyclovir)</td>
</tr>
<tr>
<td>Fenofibrate (hypercholesterolaemia)</td>
<td>Isopropyl ester of fenofibric acid</td>
<td>Lipophilic ester of fenofibric acid</td>
</tr>
<tr>
<td>Tenofovir disoproxil (antiviral)</td>
<td>Bis-(isopropyloxy-carbonyloxymethyl) ester of tenofovir</td>
<td>Bioconversion by esterases and phosphodiesterases. The oral bioavailability of tenofovir from tenofovir disoproxil is 39% after food</td>
</tr>
<tr>
<td>Lisdexamfetamine (psychostimulant)</td>
<td>L-Lysyl amide of dextroamphetamine</td>
<td>Bioconversion by intestinal or hepatic hydrolases. Reduced potential for abuse due to prolonged release of active drug</td>
</tr>
<tr>
<td>Oseltamivir (influenza)</td>
<td>Ethyl ester of oseltamivir carboxylate</td>
<td>Improved bioavailability compared to oseltamivir carboxylate, allowing oral administration</td>
</tr>
<tr>
<td>Olmesartan medoximil (hypertensio)</td>
<td>Cyclic carbonate ester of olmesartan</td>
<td>Improved bioavailability compared to olmesartan, allowing oral administration</td>
</tr>
<tr>
<td>Mycophenolate mofetil (immunosuppressant)</td>
<td>Morpholinyethyl ester of mycophenolic acid</td>
<td>Improved oral bioavailability with less variability</td>
</tr>
<tr>
<td>Latanoprost (glaucoma)</td>
<td>Isopropyl ester of latanoprost acid</td>
<td>Bioconversion by esterases. Improved lipophilicity to achieve better ocular absorption and safety</td>
</tr>
</tbody>
</table>
Prodrug strategies in drug design

11th-12th April 2012
University of Eastern Finland, Kuopio campus

Speakers
Professor Valentino Stella, University of Kansas
Dr. Victor Guarino, Ph.D., Bristol-Myers Squibb Company
Tim Gaekens, M.Sc., Johnson & Johnson
Professor Jarkko Rautio, University of Eastern Finland
Professor Hannu Raunio, University of Eastern Finland
Dr. Mikko Gynther, Ph.D., University of Copenhagen