The Interaction of Excipients with the Intestinal Transporter, OATP2B1

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ASCPT: How Inert Are Excipients?

Science at Sunrise
2017
Biopharmaceutical Classification System Class 3 Biowaivers

BCS Class 3 Drugs

Low Permeability/High Solubility Drugs

e.g., cimetidine, metformin, acyclovir, fexofenadine

Influx Transporters
Intestinal Drug Transporters

ABC Superfamily

- P-glycoprotein (ABCB1)
- BCRP (ABCG2)

SLC Superfamily (Solute Carrier Superfamily)

- PEPT1 (SLC15A1)
- OATP2B1 (SLCO2B1)
- THTR2 (SLC19A3)
Organic Anion Transporting Polypeptide, OATP2B1 - High Expression In Intestine

Diverse Substrates

- Cardiovascular Drugs (fluvastatin, talinolol)
- Hormones (estrone-3-sulfate)
- Anti-diabetic agents (glyburide)
- Antihistamines

Fexofenadine
OATPs Are Targets for Drug Drug Interactions

F. Qiang et al., Eur. J. Pharm. Sci, V 37, 2009
Influence of Apple Juice on Fexofenadine Absorption


N = 14
Fexofenadine (60 mg p.o.) +/- Apple juice (400 mL)

S-Fexofenadine Concentration, ng/mL

0 10 20 30
Time, hours

S-Fexofenadine Uptake, µL/120 min/oocyte

0.0 0.015 0.030

Apple Juice: phloridzin, phloretin, hesperidin, quercetin

OATP2B1

+ Apple Juice
**Goal:** To determine whether *excipients* used in oral drug products can inhibit OATP2B1.
Classification of 138 Oral Molecular Excipients

N = 138

CERSI Excipient Browser: http://excipients.ucsf.bkslab.org/
Characterization of OATP2B1-mediated Dibromofluorescein Uptake

Uptake time: 2 min

Km = 4 µM

DBF Uptake, pmol/min

Concentration, µM

OATP2B1 Cells

Empty Vector Cells
Screen of Oral Excipients for OATP2B1 Inhibitors

- Screen 138 Oral Molecular Excipients
- Identified 27 Inhibitors (> 50%)
- Conduct Aggregation Tests
- Conduct IC$_{50}$ Studies
- Potential Clinical Relevance
Summary of the Inhibitory Effect of 138 Oral Molecular Excipients

DBF concentration: 2 μM
Uptake time: 3 min

114 Non-inhibitors
24 Inhibitors
IC$_{50}$ Studies of Selected Excipients Identified as OATP2B1 Inhibitors

- FD&C Red No.40: $K_i = 2.5 \, \mu M$
- FD&C Yellow No.6: $K_i = 65.2 \, \mu M$
- D&C Red No. 6: $K_i = 10.8 \, \mu M$
- Neohesperidin dihydrochalcone: $K_i = 19.1 \, \mu M$
- Butylparaben: $K_i = 42.3 \, \mu M$
- Sucrose Monolaurate: $K_i = 45.5 \, \mu M$

Y-axis: DBF Uptake (% of Control)
X-axis: Concentration (log [µM])
## OATP2B1 Inhibitory Potencies of Excipients: Dyes are most potent

<table>
<thead>
<tr>
<th>Excipient</th>
<th>Ki (μM)</th>
<th>Ki (95% Confidence Intervals)</th>
<th>Aggregation</th>
</tr>
</thead>
<tbody>
<tr>
<td>FD&amp;C Red No. 40</td>
<td>2.47</td>
<td>1.83 – 3.33</td>
<td>No Aggregation @ 500 μM</td>
</tr>
<tr>
<td>FD&amp;C Orange No. 4</td>
<td>2.02</td>
<td>1.77 – 2.29</td>
<td>No Aggregation @ 100 μM</td>
</tr>
<tr>
<td>Sodium Lauryl Sulfate</td>
<td>1.88</td>
<td>1.31 – 2.72</td>
<td>No Aggregation @ 50 μM</td>
</tr>
<tr>
<td>FD&amp;C Green No. 5</td>
<td>1.47</td>
<td>1.13 – 1.92</td>
<td>No Aggregation @ 5 μM</td>
</tr>
<tr>
<td>FD&amp;C Red No. 28</td>
<td>0.96</td>
<td>0.62 – 1.5</td>
<td>No Aggregation @ 10 μM</td>
</tr>
<tr>
<td>FD&amp;C Red No. 3</td>
<td>0.84</td>
<td>0.66 - 1.06</td>
<td>No Aggregation @ 500 μM</td>
</tr>
<tr>
<td>Light Green CF Yellowish</td>
<td>0.77</td>
<td>0.69 – 0.85</td>
<td>No Aggregation @ 200 μM</td>
</tr>
<tr>
<td>Guinea green b</td>
<td>0.73</td>
<td>0.61 – 0.87</td>
<td>No Aggregation @ 5 μM</td>
</tr>
<tr>
<td>D&amp;C Red No. 27</td>
<td>0.73</td>
<td>0.43 - 1.25</td>
<td>No Aggregation @ 5 μM</td>
</tr>
<tr>
<td>Naphthol blue black</td>
<td>0.38</td>
<td>0.31 - 0.47</td>
<td>No Aggregation @ 5 μM</td>
</tr>
</tbody>
</table>
Several Dyes Have Azo Bonds that are Subject to Reduction by Intestinal Bacteria

D&C Orange No. 4 → 4-aminobenzene sulfonic acid + 1-amino-2-naphthol
E. Coli Transformed with AzoR Reduce Dyes 48 Hours After Incubation
Do the reduced metabolites inhibit OATP2B1?
D&C Orange No. 4 is a More Potent Inhibitor of OATP2B1 than Its Reduced Metabolites

D&C Orange No. 4 → 4-aminobenzene sulfonic acid + 1-amino-2-naphthol

DBF Uptake, % of Control

Log Concentration (µM)
Ki Values for Inhibition of OATP2B1 is Much Higher for the Reduced Metabolites

<table>
<thead>
<tr>
<th>Excipient</th>
<th>$K_i$ (μM)</th>
<th>$K_i$ (μM)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Metabolite 1</td>
</tr>
<tr>
<td>FD&amp;C Yellow No. 6</td>
<td>65.2</td>
<td>&gt; 200</td>
</tr>
<tr>
<td>D&amp;C Red No. 33</td>
<td>55.4</td>
<td>&gt; 50</td>
</tr>
<tr>
<td>D&amp;C Red No.7</td>
<td>10.8</td>
<td>&gt; 200</td>
</tr>
<tr>
<td>D&amp;C Brown No.1</td>
<td>3.0</td>
<td>&gt; 200</td>
</tr>
<tr>
<td>FD&amp;C Red No.40</td>
<td>2.5</td>
<td>&gt; 50</td>
</tr>
<tr>
<td>D&amp;C Orange No. 4</td>
<td>2.0</td>
<td>&gt; 200</td>
</tr>
</tbody>
</table>

Bacteria in Intestine May Reduce the Dyes and inactivate Dyes as Inhibitors of OATP2B1:
## Potential *In Vivo* Relevance

Estimated Maximum Intestinal Concentration = \[
\text{Maximum Allowable Amount} \div 250 \text{ mL}
\]

<table>
<thead>
<tr>
<th>Excipient</th>
<th>Max Amount</th>
<th>Predicted Max. Gut Con. (μM)</th>
<th>(K_i) (μM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FD&amp;C Red No. 40</td>
<td>7 mg*</td>
<td>3950</td>
<td>2.3</td>
</tr>
</tbody>
</table>

Amounts allowed in dosage forms may be much less.

* Acceptable Daily Intake (ADI), Data from WHO
# Max amount used as surfactant in beverage, CFR 21
Conclusions

- 24 excipients inhibit OATP2B1, and 114 were deemed “non-inhibitors.”
- Some excipients are predicted to inhibit OATP2B1 at allowable intestinal concentrations.
- Excipients with azo bonds may be reduced by intestinal bacteria and the reduced products are weaker inhibitors of OATP2B1.
- The Ki values of excipients will be posted on the CERSI Excipient Browser: http://excipients.ucsf.bkslab.org/.
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