Excipients Inhibit Human Organic Anion Transporting Peptide 2B1 (OATP2B1)-mediated Intestinal Uptake of Levothyroxine

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Introduction

1. Excipients can differ between brand name and generic product. Bioequivalence studies are designed to detect the impact of differences in excipients on in vivo performance of drug products. In some cases, in vivo studies are not required to demonstrate bioequivalence. Therefore, it is important to understand how excipients affect absorption in those cases.
2. It is largely unknown if FDA-approved oral excipients affect transporter-mediated drug absorption at clinically relevant concentrations.
3. OATP2B1 is a site for drug-drug and drug-food interactions.
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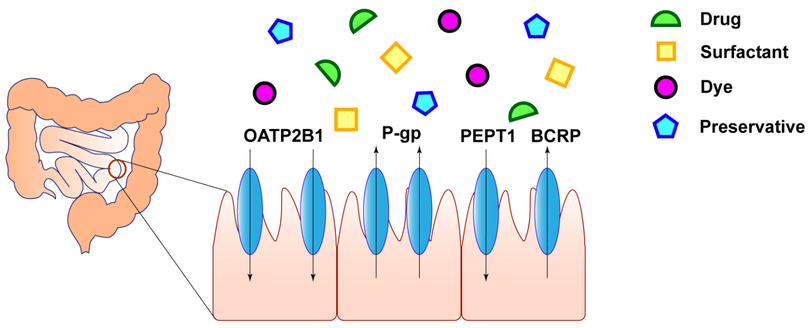

Goal

Identify excipients that inhibit OATP2B1 through medium throughput screening methods and assess their potency of inhibition.

Methods

- A fluorescent assay to assess the activity of OATP2B1 was developed.
- 138 excipients were screened at a high concentration (200 μM) to identify inhibitors of OATP2B1.
- The maximum intestinal concentrations of excipients were estimated using the equation:

$$\text{Maximum intestinal concentration} = \frac{\text{Max Amount (g) / Molar Mass (g/mol)}}{250\ \text{mL}}$$

Results

Figure 1. Overview of screening procedure and establishment of screening assay

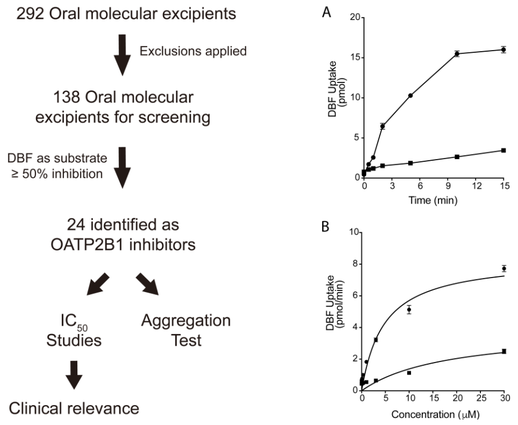

Figure 2. 24 excipients were identified as inhibitors of OATP2B1

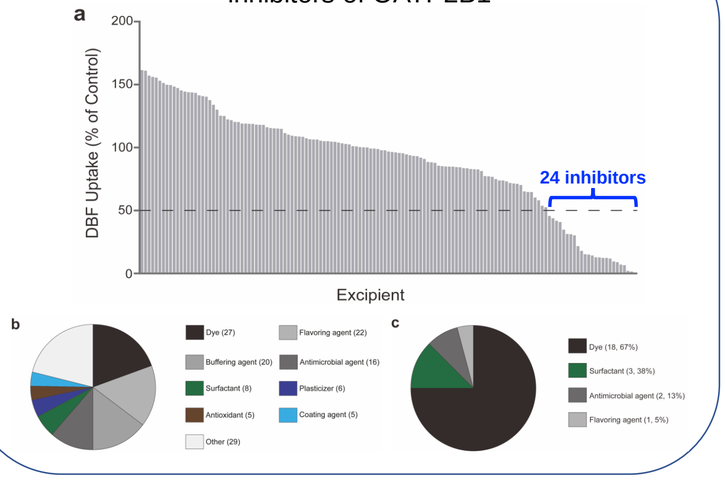

Figure 3. Inhibition curves reveal that some excipients are potent inhibitors of OATP2B1

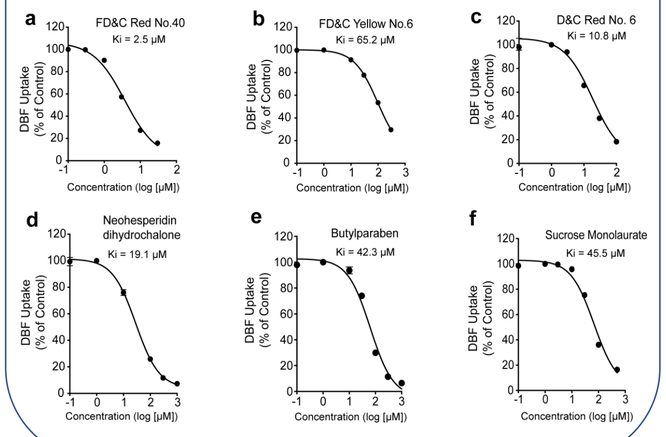

Table 1. Excipients inhibit OATP2B1-mediated levothyroxine uptake at concentrations that can potentially be clinically relevant

Excipient in formulation for a 125 mg daily dose	Predicted Max. Gut Con. (μM)	K_i (μM)	C_{max}/K_i
Mannitol	5630	> 200	ND
Lactose monohydrate	3850	> 200	ND
Sucrose	1750	> 200	ND
Lactose anhydrous	990	> 200	ND
Magnesium stearate	230	> 200	ND
Sodium lauryl sulfate	**9.8**	**2.0**	**4.9**
D&C Red No. 27	**0.8**	**1.0**	**0.8**
FD&C Red No. 40	**1.7**	**2.5**	**0.7**
FD&C Yellow No.6	**18.5**	**65**	**0.3**
D&C Red No. 30 lake	1.0	ND	ND

* Data from FDA
ND: Not determined

Conclusion

Twenty four excipients inhibit the intestinal transporter, OATP2B1. Some excipients inhibit OATP2B1 at concentrations that are predicted to be achieved clinically. Further studies are warranted to determine whether excipients affect the oral absorption of thyroxine and other drugs transported by OATP2B1.

Acknowledgement and Disclaimer

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