thereby preventing the saturation of the efflux transporters. Consequently, efflux transporters will affect the extent of oral bioavailability and the rate of absorption of class 2 compounds.

3. *Transporter-enzyme interplay in the intestines will be important, primarily for class 2 compounds that are substrates for CYP3A and phase 2 conjugation enzymes.* For such compounds, intestinal uptake transporters will generally be unimportant, owing to the rapid permeation of the drug molecule into the enterocytes as a function of their high lipid solubility. That is, the absorption of class 2 compounds is primarily passive and a function of lipophilicity. However, owing to the low solubility of these compounds, there will be little opportunity to saturate apical efflux transporters and intestinal enzymes, such as CYP3A4 and UDPglucuronosyltransferases (UGTs). Thus, changes in transporter expression and inhibition or induction of efflux transporters will cause changes in the intestinal metabolism of drugs that are substrates for the intestinal metabolic enzymes. Note the large number of class 2 compounds in Table 5.1 that are primarily substrates for CYP3A (compounds listed in bold), as well as substrates or inhibitors of the efflux transporter Pgp (indicated by superscripts S and I, respectively). Work in our laboratory has characterized this interplay in the absorptive process for the investigational cysteine protease inhibitor K77 and sirolimus, substrates for CYP3A and Pgp, and more recently for raloxifene, a substrate for UGTs and Pgp.
4. *Absorptive transporter effects will predominate for class 3 compounds.* For class 3 compounds, sufficient drug will be available in the gut lumen owing to good solubility, but an absorptive transporter will be necessary to overcome the poor permeability characteristics of these compounds. However, intestinal apical efflux transporters may also be important for the absorption of such compounds when sufficient enterocyte penetration is achieved via an uptake transporter.

RECOMMENDED READING

Dissolution

Batchelor, H. K. et al. (2014). "Paediatric oral biopharmaceutics: Key considerations and current challenges." *Adv Drug Deliv Rev* 73:102–126.

The complex process of oral drug absorption is influenced by a host of drug and formulation properties as well as their interaction with the GI environment in terms of drug solubility, dissolution, permeability, and presystemic metabolism. For adult dosage forms the use of biopharmaceutical tools to aid in the design and development of medicinal products is well documented. This review considers current literature evidence to guide development of bespoke pediatric biopharmaceutics tools and reviews current understanding surrounding extrapolation of adult methodology into a pediatric population. Clinical testing and the use of in silico models were also reviewed. The results demonstrate that further work is required to adequately characterize the pediatric GI tract to ensure that biopharmaceutics tools are appropriate to