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Linking the lab to the patient: Tools for optimizing oral drug delivery

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In the development of new drugs as well as new formulations of existing products (including generic products), it is of great interest to be able to predict to what extent the drug can be absorbed from the gastrointestinal (GI) tract and how the formulation and dosing conditions may affect the absorption profile. The hypothesis behind Biorelevant release testing is that "the closer the test conditions can simulate the gastrointestinal environment, the better the prediction will be." Typical aspects of GI physiology, which can influence drug bioavailability, are the composition of the GI fluids (which affects various processes including release from the dosage form and stability of the drug), GI motility and hydrodynamics (transit characteristics of the dosage form, release from the dosage form etc.), and permeability of the GI mucosa to the drug as a function of location in the GI tract, and gut wall metabolism. While release from the dosage form can be addressed with Biorelevant release tests, which seek to reproduce compositional and hydrodynamic conditions at various locations within the GI tract, the interplay of release with gut wall permeability, gastric emptying and first pass metabolism are difficult to reflect in these *in vitro* release tests. By coupling the release test results with a physiologically based pharmacokinetic (PBPK) model that details GI physiology as well as post absorptive events in the body, there is great value added in terms of predicting *in vivo*

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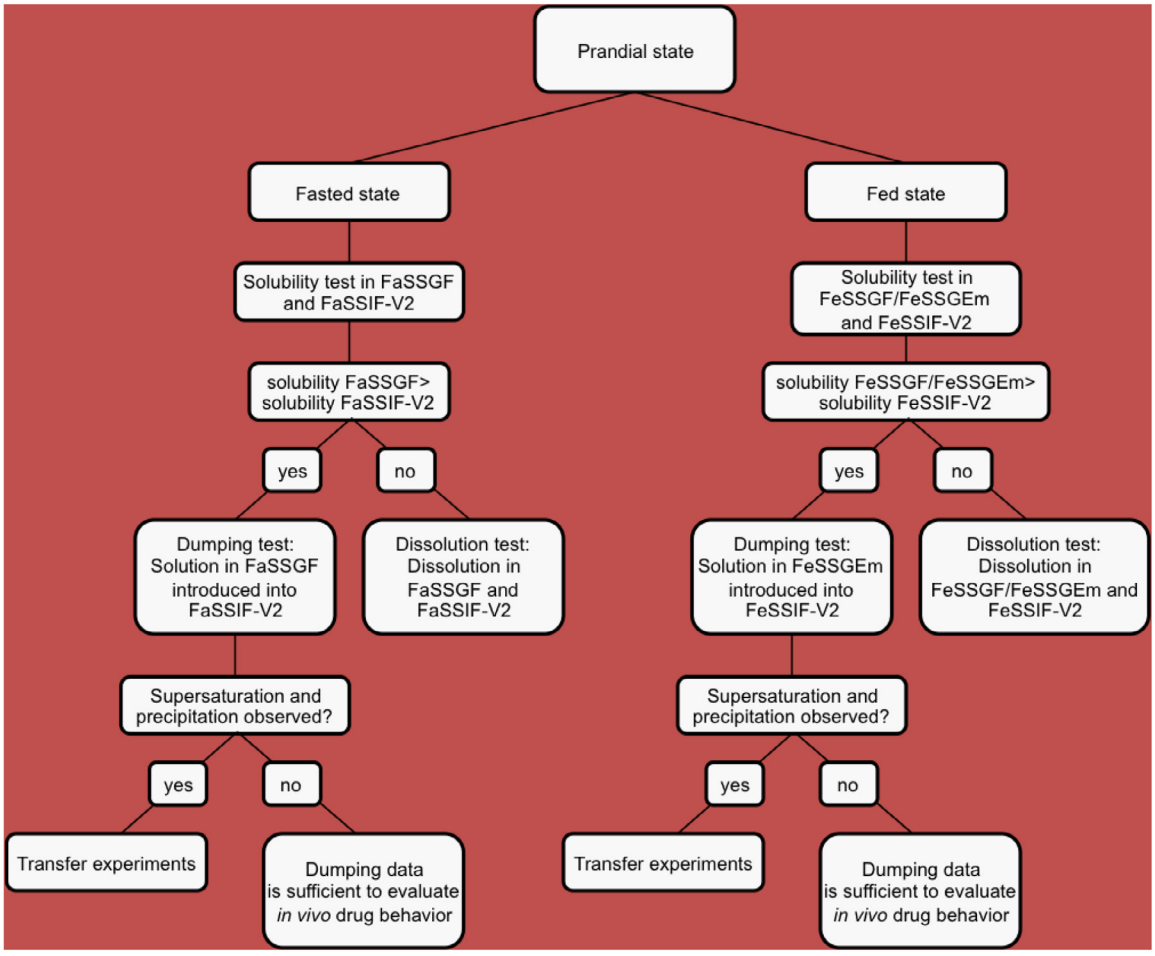

Fig. 1 – The Berlin Decision Tree for development of poorly soluble weak bases (with copyright permission from M. Berlin).

performance of the drug. This presentation will highlight the physiological conditions in the GI tract relevant to drug and formulation performance in the fasted and fed states, describe the Biorelevant release test conditions that can be used to simulate these and show two case examples (both poorly soluble weak bases) where coupling Biorelevant release testing with PBPK modelling has successfully predicted plasma profiles of the drug after oral administration.

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