Predicting dose-dependent fraction absorbed via a mechanistic absorption model and machine learning

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INTRODUCTION

- Drug dissolution and absorption are crucial in oral drug delivery
- The Advanced Compartmental Absorption and Transit (ACAT™) model[1] mechanistically estimates the percent of dose (%Fa) absorbed into the gut wall
- ADMET Predictor®[2] ANNE models are used to predict inputs parameters of the ACAT model
- 978 structures of orally delivered drugs were downloaded from the ChEMBL database[3]
- %Fa was predicted for 1, 10, 100, and 1000 mg immediate release tablets
- The Biopharmaceutical Classification System[4] (BCS) was used to help analyze dose dependency

METHODS

ACAT Model

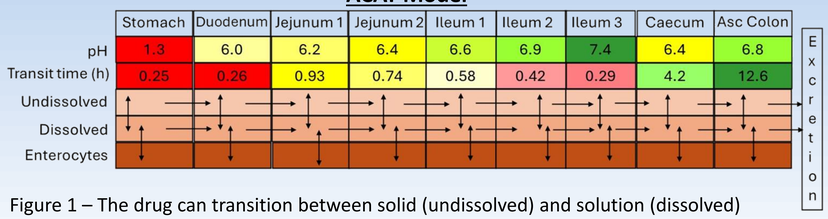


Figure 1 – The drug can transition between solid (undissolved) and solution (dissolved) phases. The precipitation model follows first-order kinetics with a 25 µm particle size and a mean precipitation time of 900 seconds. Note that the impact of transporters was not included in this study. If present, transporters can also cause dose dependency.

Predicted Properties

- ANNE models were used to predict inputs from the 2D structure of the drug
- ACAT input parameters are native aqueous solubility (S+Sw), pKa (S+pKa), salt solubility factor (SolFactor), human jejunal permeability (S+Peff), logP (S+logP), and fasted simulated intestinal fluid solubility (S+FaSSIF)

Oral drug dataset

- Queried ChEMBL for approved, small molecule drugs on March 1, 2024
  - Downloaded ChEMBL ID, SMILES, name, oral, and prodrug fields; 3,312 SMILES downloaded
- Removed duplicates, non-oral drugs, and prodrugs
  - 978 remained

BCS

- Classifies compounds based on low or high permeability and dose number
- Permeability is based on S+Peff with a 0.5 x 10^{-4} cm/s cutoff
- The dose number (ml) is the dose (mg) divided by intrinsic solubility (higher numbers have lower solubility) and the cutoff is 250 ml

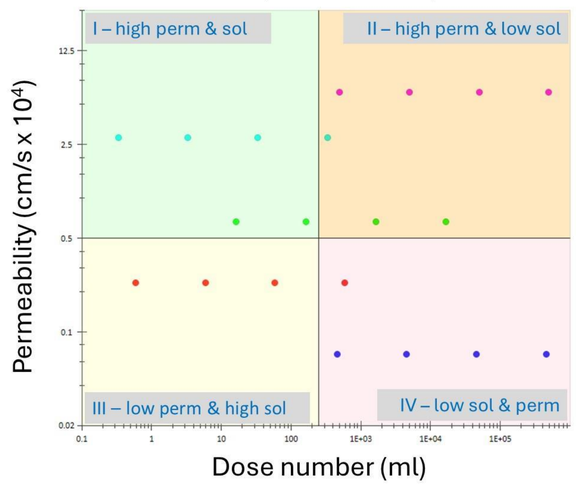


Figure 2 - BCS classes for 5 drugs at 4 doses (1, 10, 100, and 1000 mg). Increasing the dose will move the point to the right and can change the BCS class.

RESULTS

Fraction Absorbed Plots of Various Doses

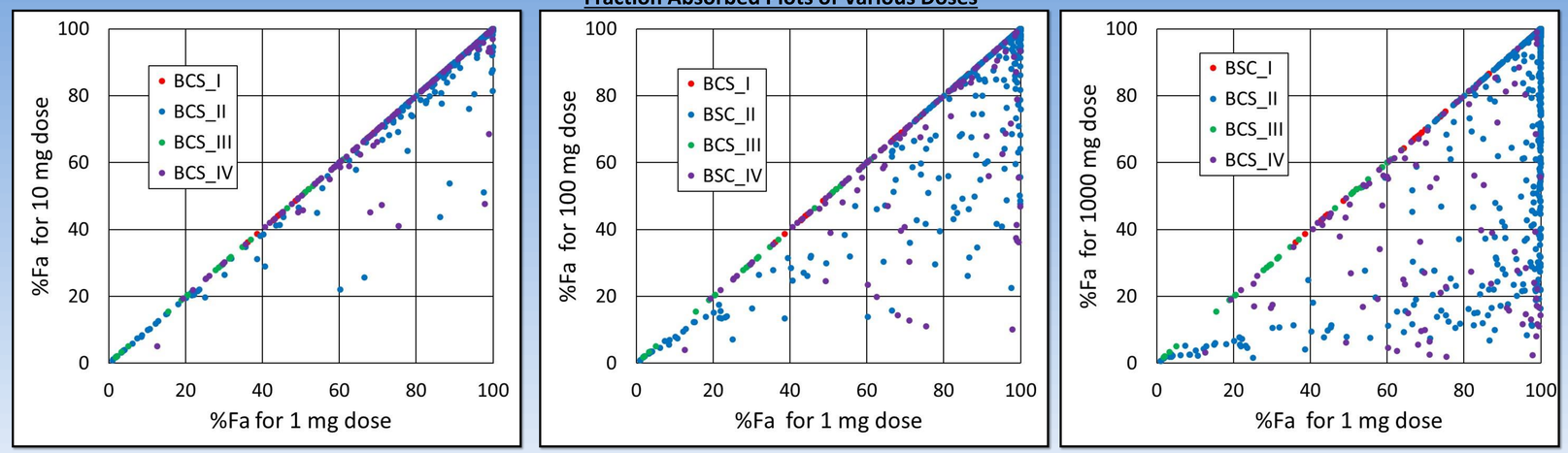
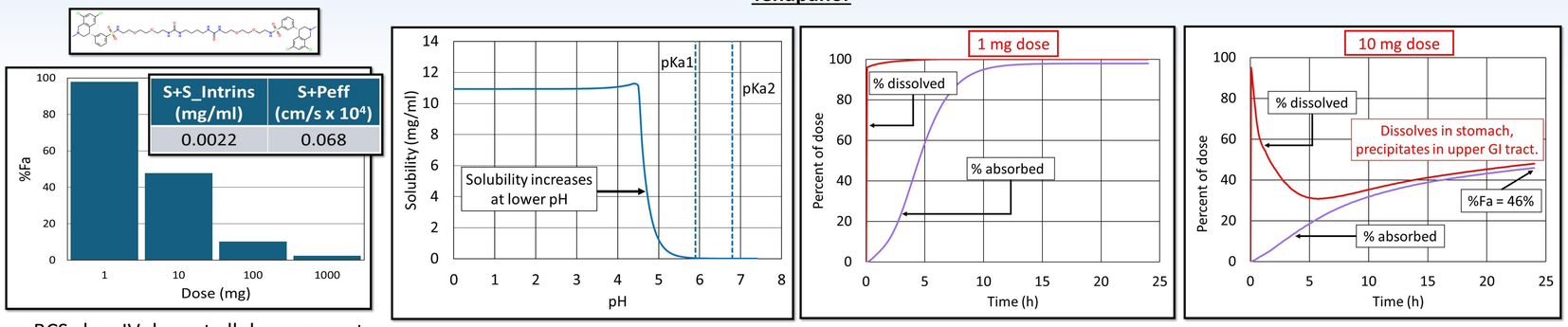


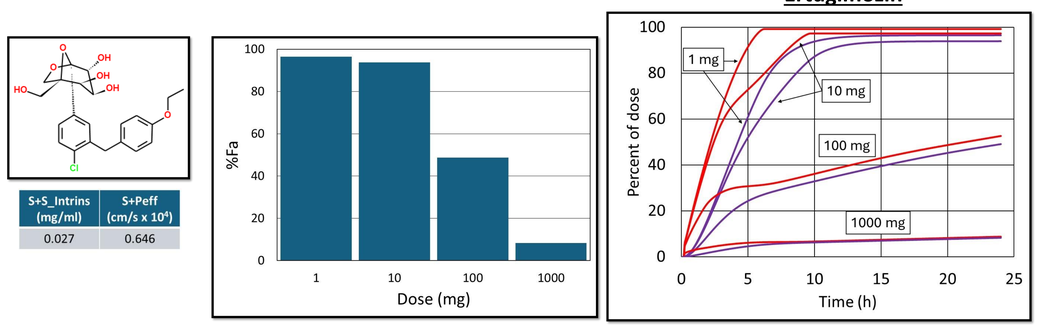
Figure 3 - Plots of %Fa for 10 (left), 100 (middle), and 1000 (right) mg dose versus 1 mg dose. The points are colored by BCS class for the 1000 mg dose. Off-diagonal elements indicate dose dependency. Note, that the only off-diagonal elements are BCS classes II and IV, i.e., low solubility. Thus, low solubility is an important factor in dose dependency.

Tenapanor



- BCS class IV drug at all dose amounts
- The drug is indicated for irritable bowel syndrome, so it is beneficial for the compound to stay in the gastrointestinal tract
  - Recommended dose is 50 mg and yields a predicted %Fa of 17%

Ertugliflozin



- BCS I at 1 mg dose and class II at higher doses
- Large drop in the percent dissolved and absorbed from the two lower doses to the two higher doses
- Illustrates the importance of selecting the optimal dose to balance dissolution and absorption

CONCLUSIONS

- %Fa depends on an interplay between pKa, logD, solubility, and permeability
- BCS classes I and III do not exhibit dose dependency
- BCS classes II and IV exhibit dose dependency, indicating that low solubility is the main contributing factor

REFERENCES

[1] GastroPlus 9.9, Simulations Plus, Inc. Lancaster CA.
[2] ADMET Predictor 11.0, Simulations Plus, Inc. Lancaster CA.
[3] Zrazil B et al. Nucleic Acids Research, 2024, 52, D1, D1180–D1192, https://doi.org/10.1093/nar/gkad1004.
[4] Amidon GL et al. Pharm Res. 1998, Mar;12(3):413-20.

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