Application of HT-PBPK Modelling for developing an IVIVE of Oral Permeability in OSPsuite

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Introduction

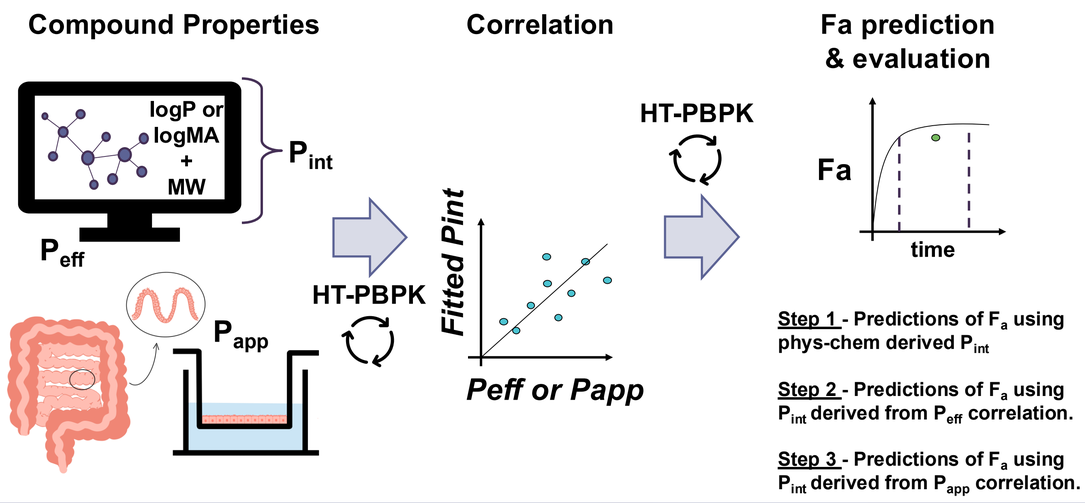
Physiologically Based Pharmacokinetic (PBPK) modeling is a powerful tool for predicting drug absorption, distribution, metabolism, and excretion (ADME). Predicting *in vivo* permeability remains a key step in oral drug absorption modeling. In PBPK models, intestinal permeability can be derived from physicochemical properties, translated from *in vitro* permeability assays or *in vivo* (i.e., solution PK) data.

The main objective of this work was to leverage a High-Throughput PBPK (HT-PBPK) framework to systematically evaluate and refine an in vitro–in vivo extrapolation (IVIVE) approach for oral permeability for the Open Systems Pharmacology (OSP) software.

Methods

- Compound files were created with data gathered from the literature, including molecular weight, lipophilicity, and solubility. Within PK-Sim®, the intestinal wall's transcellular specific permeability (*i.e.*, $P_{int,default}$) is calculated from its physicochemical properties (MW, lipophilicity).
- A HT-PBPK modeling strategy (R4.4.1, with OSPsuite R, OSPSuite.ParameterIdentification packages) was used to:

1. Fit transcellular permeability to measured F_a (i.e., P_{int} was optimized through parameter identification);
2. Derive correlations between fitted P_{int} *vs* P_{eff}, and fitted P_{int} *vs* P_{app} (1, 2);
3. The correlations were tested for predicted *vs* measured fraction absorbed (F_a) 4h and 24h. F_a predictions were performed with literature solubility (*i.e.,* original) and assuming formulations that behave as solutions (solubility was artificially increased to an arbitrary non-limiting high value).



Step 1 - Predictions of F_a using phys-chem derived P_{int}

Step 2 - Predictions of F_a using P_{int} derived from P_{eff} correlation.

Step 3 - Predictions of F_a using P_{int} derived from P_{app} correlation.

Results

- Step 1 - The predicted F_a was mostly underpredicted ($R^2 \leq 0.5$, with most points falling below the line of identity) when using the default calculated permeability by PK-Sim®, $P_{int,default}$, as presented in Figure 1.

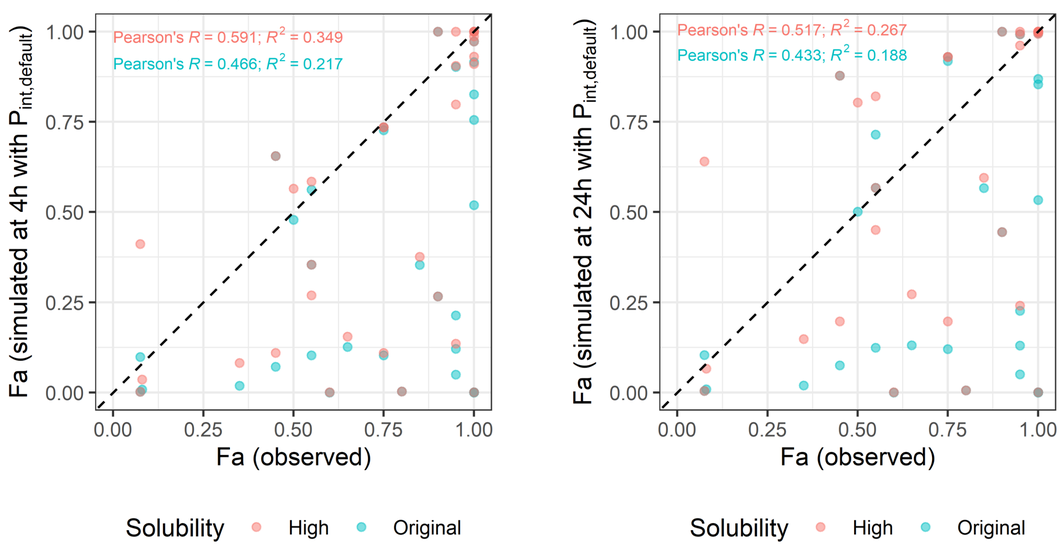


Figure 1: Correlation between predicted and observed F_a at 4h (left-panel) and 24h (right-panel) (with calculated $P_{int,default}$ calculated from lipophilicity and MW without fitting).

- After fitting P_{int} using the HT-PBPK workflow, an optimal correlation between observed and predicted Fa was achieved, highlighting the success of the fitting process (data not shown).
- Fitted P_{int} was correlated with P_{eff} (Figure 2), P_{app} at pH 6.5 (Figure 4), and pH 7.4 (data not shown).
- Regressions with fitted P_{int} - P_{eff}/P_{app} were performed: 1. with all compounds included and 2. by removing compounds with observed F_a=1 (which were associated with a large confidence interval of fitted P_{int}, highlighting that the values were not well defined).

- Step 2 - F_a predictions presented in Figure 4 were derived from the regression between fitted P_{int} *vs* P_{eff} (Figure 5), excluding compounds with F_a=1. Similar results were achieved when all compounds were included (data not shown).
- Solubility input influenced the correlation of pred *vs* obs F_a (Figure 3-4). A high solubility leads to a better correlation of F_a than when using the original solubility input (R^2~0.7 *vs* R^2 =0.142-0.196, respectively).

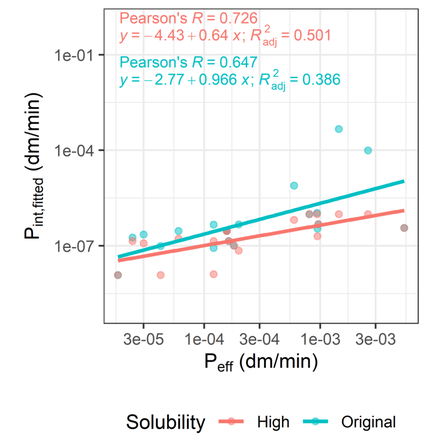


Figure 3: Correlation between $P_{int,\ fitted}$ and P_{eff}.

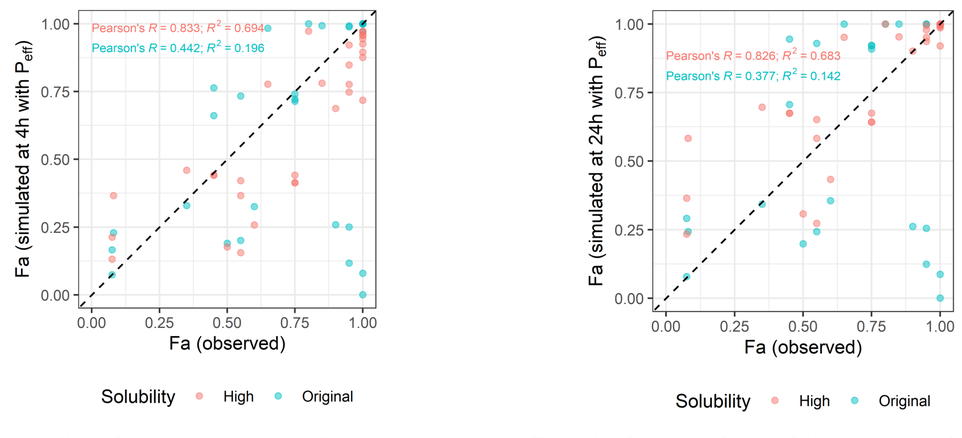


Figure 4: Correlation between predicted and observed F_a at 4h (left-panel) and 24h (right-panel) (with P_{int} calculated from the correlation between fitted P_{int} and P_{eff} presented in Figure 3).

- Step 3 - F_a predictions derived from the regression between fitted P_{int} *vs* P_{app} (Figure 5) were slightly better for P_{app} from pH 6.5 (Figure 6, R^2 = 0.784 at 4h) than pH 7.4 (data not shown, R^2 = 0.531 at 4h).
- Excluding compounds F_a=1 from the regression fitted P_{int} *vs* P_{app} improved significantly the F_a prediction.
- Differences were observed between predicted F_a at 4h *vs* 24h, with a trend to overestimate the role of colonic absorption.

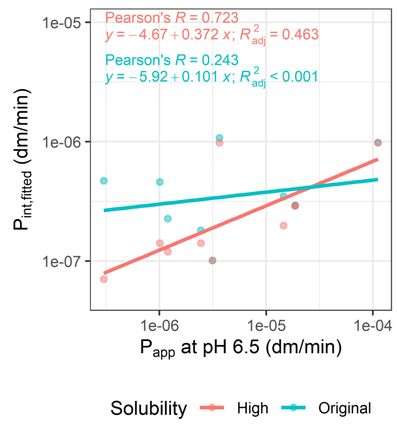


Figure 5: Correlation between $P_{int,\ fitted}$ and P_{app} at pH 6.5.

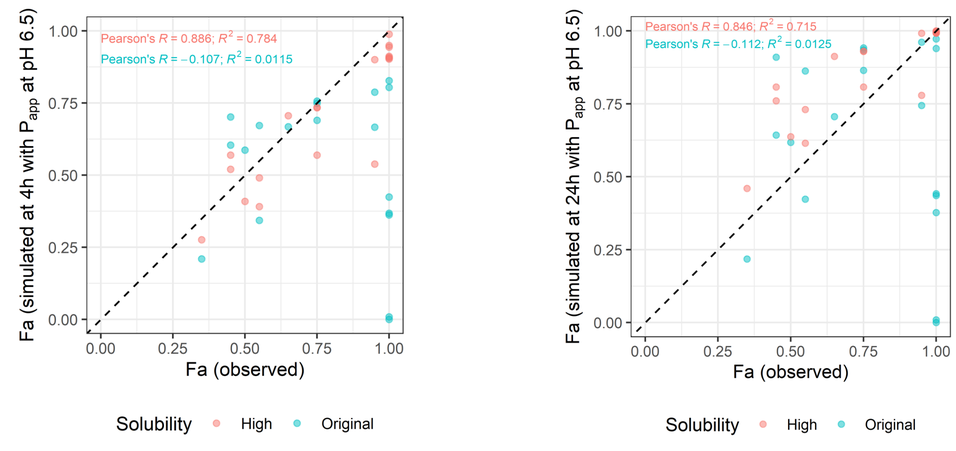


Figure 6: Correlation between predicted and observed Fa at 4h (left-panel) and 24h (right-panel) (with P_{int} calculated from the correlation between fitted P_{int} and P_{app} at pH 6.5 presented in Figure 5).

Conclusion

Our findings provide insights into the mechanistic drivers of permeability and oral absorption in OSP predictions and highlight the advantages of **HT-PBPK in rapidly assessing multiple compounds and scenarios**. **Overall, F_a prediction with OSP improved when informed by P_{eff} and P_{app}.** As further datasets are collected (e.g., MCDK, PAMPA, etc.), expansion of the applicability domain can be quickly achieved. In the future, HT-PBPK modeling coupled with artificial intelligence tools can enable improved predictions of intestinal permeability and tissue partitioning. The approach investigated in this work enhances the reliability of OSP PBPK models for biopharmaceutics risk assessment, formulation optimization, and regulatory decision-making, ultimately supporting more efficient drug development.

References

[1] Lennernäs H. Xenobiotica. 2007 Oct-Nov;37(10-11):1015-51. doi: 10.1080/00498250701704819. PMID: 17968735.
[2] Sun D, Lennernas H, Welage LS, Barnett JL, Landowski CP, Foster D, Fleisher D, Lee KD, Amidon GL. Pharm Res. 2002 Oct;19(10):1400-16. doi: 10.1023/a:1020483911355. PMID: 12425456.

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