Impact of Variability in Estimates of Drug Diffusion Coefficient on the Prediction of Fraction Absorbed from the Gut (fa) Using the ADAM Model (Simcyp v7.1)

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Introduction

For immediate release (IR) solid dosage formulations the rate of dissolution from drug particles can be predicted using diffusion layer boundary models [1,2]. These models require, amongst other factors, knowledge of the drug diffusion coefficient (D). When dissolution is rate limiting in the absorption process accurate knowledge of D may impact upon the predicted rate and extent of absorption.

A variety of methods for estimating aqueous D from readily available physicochemical properties are available. The predictive performance of these methods was compared using a dataset collected from the literature. Sensitivity analysis was then performed using simulated virtual populations to assess the impact of variability in particle size and D on prediction of the fraction of drug absorbed into enterocytes (fa).

Methods

Experimentally measured values of the diffusion coefficients of 151 compounds (42 drugs) were collated from the literature. The means and ranges of D, log P and MW values are shown in Table 1.

Table 1. MW, logP and D values of the data set.

	min		*max*		*Mean*	
	all	***drugs***	***all***	***drugs***	***all***	***drugs***
MW	*32.0*	*60.1*	*522.7*	*500.4*	*193.0*	*326.0*
logP	*-5.41*	*-2.11*	*8.90*	*8.90*	*1.2*	*3.26*
D x10^{-4} [cm^2/min]	*1.21*	*1.62*	*10.02*	*8.28*	*4.81*	*3.89*

The predictive performances of the methods of Avdeef [3], Draper [4], Polson [5] and Seki [6] were then evaluated. To explore the sensitivity of predicted fa from *in vitro* data to D, the Advanced Dissolution, Absorption and Metabolism (ADAM) model [7], as implemented in Simcyp® V7.1 (www.simcyp.com), was used to simulate the absorption of caffeine, felodipine and alprazolam. The predicted values of D along with an average value of 6 suggested in [2] were considered. Initially, the simulations were undertaken using a default value for diffusion layer thickness (30µm) and the particle size was set to 50µm. Further simulations were carried out for a range of particle sizes varying from 1 µm to 100 µm using a North European Caucasian virtual population of 100 healthy subjects.

Results

The performance of the Avdeef and Draper model was found to be superior to that of the other models (Table 2).

Table 2. Predictive performance of different methods of estimating D. (APE = absolute prediction error; RMSE = root mean square error)

Method	Equation	APE	RMSE
Avdeef	$\log D = \log(600000) + (-4.113 - 0.4609 \log MW)$	0.673	0.866
Draper	$\log D = \log(600000) + (-4.13 - 0.448 \log MW)$	0.674	0.863
Polson	$D = 0.06 * (274/MW^{1/3} + 165/MW^{2/3} + 1700/MW)$	0.798	0.935
Seki-1	$\log D = \log(600000) + (-4.059 - 0.434 \log MW)$	1.338	1.608
Seki-2	$\log D = \log(600000) + (-0.374 \log MW - 0.04 \log P - 4.109)$	2.312	2.935

As expected, the predicted fa value of caffeine, a highly soluble drug, was insensitive to the value of D - even two-fold changes to D had no impact. In contrast, for alprazolam and felodipine, both relatively poorly soluble compounds but with high and low permeabilities, respectively, ($P_{eff,man} \approx 9 \times 10^{-4}$ cm/s *vs* $\approx 2 \times 10^{-4}$ cm/s), fa was sensitive to the value of D (Figures 1-4). For these drugs, dissolution rate-limits the absorption process and it is expected that differences in D are likely to propagate to predicted fa values. When the values of both particle size and diffusion coefficient were varied, considerable differences in predicted fa were observed (Figures 3 and 4). In particular, the value of fa was more sensitive at larger particle sizes (60 – 100 µm).

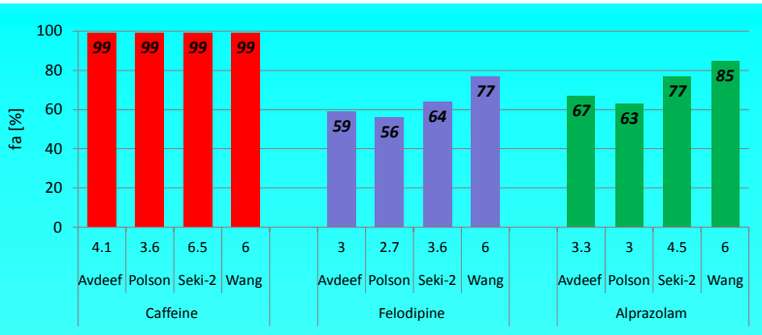

Figure 1. fa values (as %) of the test drugs determined using values of D predicted by different equations.

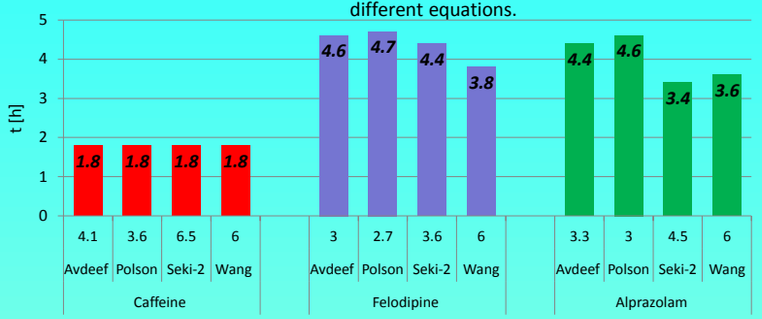

Figure 2. Time (hours) to reach 90% absorption of the test drugs determined using values of D predicted by different equations.

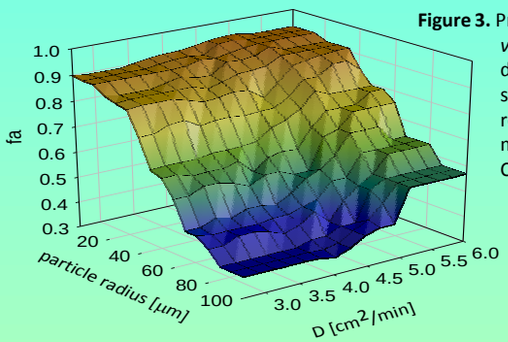

Figure 3. Predicted fa of felodipine *vs*. particle size and diffusion coefficient. The simulations were run for a representative healthy, male North European Caucasian population

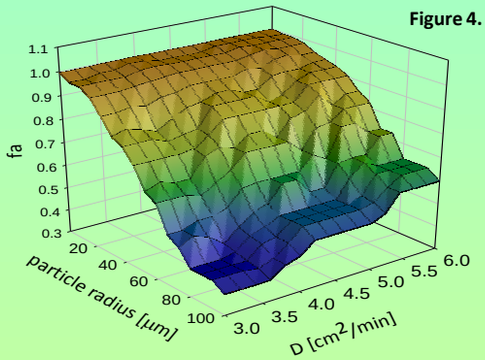

Figure 4. Predicted fa of alprazolam *vs*. particle size and diffusion coefficient. The simulations were run for a representative healthy, male North European Caucasian population

Conclusions

Of the models tested, that of Avdeef and Draper provided the best prediction of aqueous D. Estimates of the rate and extent of oral absorption, determined using ADAM, were found to be sensitive to both D and particle size for poorly soluble drugs. Accurate values of D are necessary to provide reliable predictions of fa for class II and III compounds of the Biopharmaceutical Drug Classification [11]. The findings also reinforce the need for sensitivity analysis to identify rate-limiting processes when simulating oral drug absorption.

References

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