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Quantitating the Contributions of the Particle Drift Effect to In-vitro FLUX and the Application of Particle Drift Flux to Predictive Modelling

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PURPOSE

The particle drift effect (PDE) has been previously cited[1] as an explanation for the apparent in-vivo dose dependency for some solubility/permeability limited APIs which exhibit a predominant unstirred water layer (UWL) limitation to their absorption. Celecox, a formulated product of the API celecoxib (CEL), is assayed for flux in this study to investigate the influence of in-vitro dosage on the observed flux when the donor compartment is loaded beyond the solubility limit of the API.

The applicability of flux values for assessing the in-vivo influence of the particle drift effect in predictive modelling is also explored.

METHOD(S)

MicroFLUX™ Dissolution/Permeability Assays

Flux assays were carried out using the MicroFLUX™ two-compartment dissolution/permeability testing apparatus (Pion Inc., Billerica, MA, USA). Quantitation of the API of each formulation was performed by a Rainbow R6 FO spectrometer.

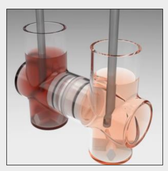

Figure 1. MicroFLUX™ glass pair vessel. The apparatus consists of two glass chambers separated by a lipid coated PVDF membrane. pH 7.4 sink buffer containing solubilising agents is used to maintain sink conditions in the acceptor vessel.

Flux assays were performed at least in triplicate using pH 6.5 V1 FaSSIF as the donor medium, at a variety of API donor loadings above the API solubility. Donor loadings were scaled to match the dose/volume ratio of the comparison set of in-vivo CEL bioavailability data, presuming a human intestinal volume of 150 mL.

In-silico Modelling

Concentration vs time results from the MicroFLUX assays were processed in AuPRO version 7.1.0.767, and then imported to Predictor v1.0. Predictions of in-vivo Fa% were generated using the fraction absorbed calculation of the Pion Predictor™ software package using the imported flux data, presuming a Human intestinal transit time of 210 minutes.

Other required inputs to the fraction absorbed model such as the effective permeability of the API and the apparent permeability contribution of the undissolved CEL solids were separately calculated from the source flux data. Predictions were determined with and without application of the 'PDE modelling' function of Predictor v1.0.

RESULT(S)

In-vitro Dissolution/Permeability Assays

The PDE postulates that the apparent permeability of an API can increase when particles of the API move into and dissolve inside the UWL between bulk media and a membrane barrier, increasing the API concentration in the UWL and yielding enhanced permeability. This UWL concentration increase results in a reduction of the concentration gradient[2] between the bulk of solution and the UWL, which plateaus when the API solubility is reached in the UWL.

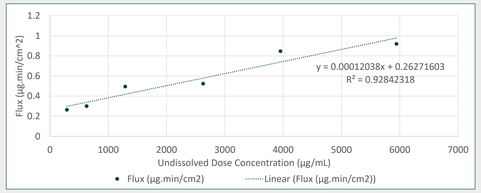

Figure 2. In-vitro flux values plotted vs the concentration of the undissolved portion of the CEL dose. The slope becomes the apparent permeability of the undissolved material input to the PDE function of the Predictor model.

The results obtained from the flux assays exhibited increasing flux beyond the solubility limitation of CEL, and showed a dose dependency on the flux values, where flux increased proportionally to the load of undissolved material. Figure 2 shows a linear plot of the measured flux values against the undissolved CEL API concentration.

Fraction Absorbed Predictions

The slope of the best fit line of the flux vs undissolved dose concentration data was applied in the PDE modelling function of the Predictor program, to upscale the observed in-vitro particle drift behaviour and estimate the proportion of the in-vivo flux arising due to particle drifting for a given amount of undissolved material in the intestinal lumen. The results of the Predictor model are shown in figure 3 for Celecox at each dose level. Without correcting for the influence of particle drift on the in-vivo flux, the overall absolute fraction absorbed is underestimated by approximately 1.7-fold for the 50 mg dose. The observed discrepancy in the Prediction increases with the dosage.

The results for all tested dose levels are presented in figure 4 and table 1, including the Predictor Fa% output with and without correction for the PDE, and in-vivo human Fa% data[3] for Celecox. A notably improved correlation to the in-vivo data is observed for the fraction absorbed predictions when the particle drift effect is accounted for, especially at higher loadings where the effect is more significant.

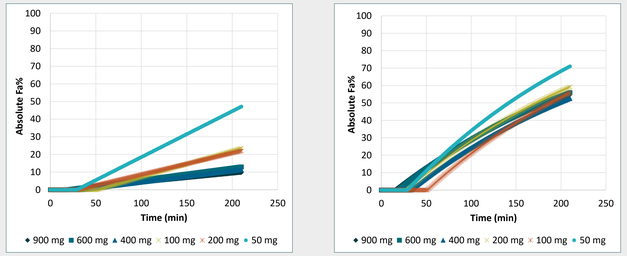

Figure 3. Celecoxib absolute fraction absorbed vs time plots generated by Predictor v1.0, the standard Fa% model is shown on the left, and the right plot is calculated considering the permeability increase associated with UWL diffusion of undissolved CEL using the PDE modelling function.

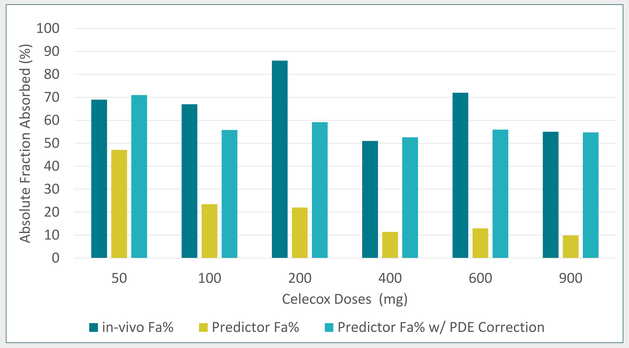

Figure 4. In vivo Celecox data at variable dosage vs predictions with and without accounting for particle drifting.

Celecox Dose (mg)	Predictor Fa%	Predictor Fa% w/ PDE Correction	in-vivo Fa%
50	47.12	70.98	69
100	23.48	55.78	67
200	22.02	59.2	86
400	11.39	52.62	51
600	12.94	55.93	72
900	9.81	54.75	55

Table 1. In vivo Celecox data at variable dosage vs predictions with and without accounting for particle drifting.

CONCLUSION(S)

The data presented here illustrates that for solubility/permeability limited APIs, with UWL limited absorption, predictions of in-vivo absorption based on in-vitro flux results are susceptible to underestimation in situations where intestinal absorption is driven in part by small particles, causing an effective increase in the UWL permeability of the drug.

In-vitro flux measurements are a capable tool in the assessment of the influence of particle drifting on measured flux values, and in-vitro observations of particle drifting have applicability in the correction of predicted in-vivo behaviour for this phenomenon.

REFERENCE(S)

1. K. Sugano, Possible reduction of effective thickness of intestinal unstirred water layer by particle drifting effect, International Journal of Pharmaceutics 387 (2010) 103–109.
2. Siddhi S. Hate, Laura I. Mosquera-Giraldo, Lynne S. Taylor, A Mechanistic Study of Drug Mass Transport from Supersaturated Solutions Across PAMPA Membranes, Journal of Pharmaceutical Sciences 111 (2022) 102−115.
3. Sugano K. Biopharmaceutics Modelling and Simulations p266-321 (Aug 2012).