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Experimental and Mathematical Analysis of Hepatic Uptake

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Introduction:
To investigate the nonlinear kinetics of *in vitro* hepatic uptake the OATP substrate, Pitivastatin, was used as a probe. Experiments were conducted using freshly isolated rat hepatocytes, utilising the 'oil spin' methodology described by Hassen *et al* [1]. Briefly, freshly isolated rat hepatocytes were incubated with Pitvastatin (5–300µM). At 10 s, 30 s, 50 s and 70 s aliquots were spun through a silicone oil layer to separate the hepatocytes from the media. $[Pitivastatin]_{hepatocyte}$ was detemined using LCMSMS.
Results:
Uptake to rat hepatocytes was saturable and progressed according to Michaelis-Menten kinetics. The K_m and V_{max} of Pitvastatin were 2050 pmols/min/10^6 cells and 33 µM respectively, which was in in good agreement with other literature reports [2].
Mathematical Modelling:
A nonlinear pharmacokinetic model has been derived to characterise the uptake process. A structural identifiablity analysis was performed on the model to establish that all unknown parameters could be identified from the experimental observations available. The model was then subsequently used for parameter estimation and model validation using the data collected. Sensitivity analysis and model robustness analyses were also performed. Once fully validated the model has the potential to perform robust, predictive simulations to ascertain optimal levels of uptake and the effects of the use of appropriate inhibitors.
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