Simulation of Sublingual and Gastrointestinal Absorption of Nifedipine

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Abstract

Purpose: To develop an integrated model for drug absorption from the oral cavity. The model simulates combined absorption of a drug from both the oral cavity and the gastrointestinal tract.

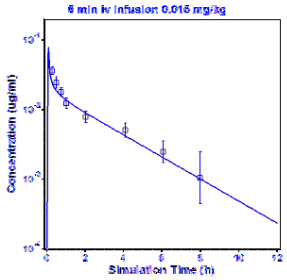
Methods: GastroPlus™ 5.3 with the PBPKPlus™ Module (Simulations Plus, Inc., Lancaster, CA) was used to simulate adult human plasma concentration time (Cp-time) profiles of nifedipine when administered as a 1 mg intravenous (IV) infusion, 10 mg oral capsule (PO), 10 mg oral solution held sublingually (SL) for 7 min and then swallowed, and 10 mg oral solution held sublingually for 20 min and expectorated. A physiologically-based pharmacokinetic model (PBPK) based on adult human physiology was used in all simulations. Tissue/plasma partition coefficients were calculated using *in silico* physicochemical properties (ADMET Predictor™, Simulations Plus, Lancaster, CA) combined with *in vitro* measured values where available. Cp-time data from an IV infusion dose were used to fit the systemic clearance model, which was then used in all PO and SL dose simulations. Cp-time profiles after expectorated SL and PO doses were used to calibrate the absorption and first pass extraction of drug from the oral cavity and the gastrointestinal tract, respectively. The combination of these absorption parameters was then used to simulate the SL dose swallowed after 7 min.

Results: The Cp-time profiles for all the dosage forms were successfully modeled with a single absorption-pharmacokinetic model incorporating sublingual and gastrointestinal absorption with physiologically-based pharmacokinetics.

Conclusion: The developed generic model can be used for simulation of a variety of dosage forms that deliver drug into the oral cavity. Integration of the new model with the well-established gastrointestinal absorption model (ACAT) provides a mechanistic interpretation of complex formulation issues.

1.Calibrate pharmacokinetics:

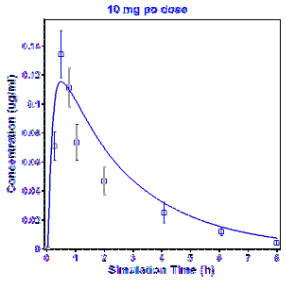
A Physiologically-based pharmacokinetic (PBPK) model for a typical 23-year-old adult was used to describe the pharmacokinetics of nifedipine. Tissue distribution was modeled based on tissue:plasma partition coefficients calculated using a modified Rodgers & Rowland equation [1-2]. Volume of distribution was 50L. The clearance of Nifedipine is assumed to be mostly due to hepatic metabolism. Liver clearance was fitted to the observed Cp-time profile after an IV dose [3]. The fitted clearance was 20 L/h. Calculating intrinsic clearance from *in vitro* Km and Vmax values [8] as Vmax/Km and converting it into plasma clearance yields 41L/h.

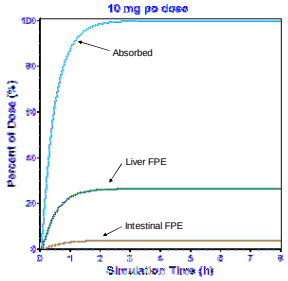


The two-fold difference between these two clearance values corresponds to ~2 fold difference in the expression of CYP 3A4 in livers used in the present *in vitro* study (average ~216 pmol/mg MP) and reported average expression of CYP 3A4 [9] in caucasian population (~111 pmol/mg MP). This calibrated PBPK model was used in all subsequent simulations (oral dosing, sublingual expectorated dose, and sublingual swallowed dose).

2. Calibrate intestinal absorption and first pass extraction:

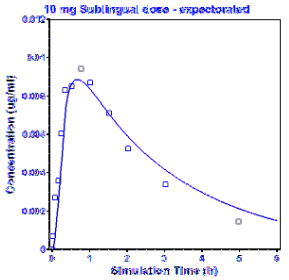
The default GastroPlus Human-Physiological-Fasted gut model was used to simulate intestinal absorption. CYP 3A4 was added to gut to account for possible intestinal first pass extraction [4-6]. The *in vitro* Km value for nifedipine interaction with CYP 3A4 was used as measured [8]. Vmax was estimated from the clearance adjusted for the IV dose and the *in vitro* Km value. The Km and Vmax values used in simulations were: Km = 8.76 mg/L; Vmax = 0.063 mg/s. In order to match the rapid initial rise in Cp-time, a high permeability through the gastrointestinal mucosa was used. Simulated fraction absorbed is 100%, intestinal first pass extraction is 4% and liver first pass extraction is 23%.





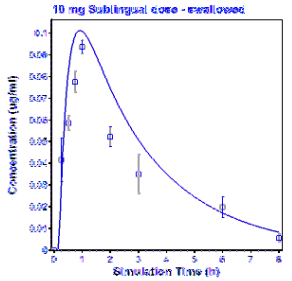
3. Calibrate sublingual absorption and first pass extraction:

The sublingual absorption was calibrated against the data after sublingual dose which was expectorated after 20 minutes [7]. Sublingual absorption is slower than intestinal absorption (Sublingual Tmax ~45 min, Oral Tmax ~ 30min). The initial rise in Cp-time and low plasma concentration could be matched only if significant first pass extraction in oral mucosa was assumed (~60% of the absorbed amount). Simulated fraction absorbed is 15%, simulated bioavailability is 6%. Note that simulated combined intestinal and liver first pass extraction after standard PO solution was only 27%.



4. Predict the Cp-time profile for combined sublingual and intestinal absorption:

Fitted parameters for Cp-time profiles after an IV dose (pharmacokinetics), a PO solution dose (gastrointestinal permeability), and a sublingual dose that was expectorated (sublingual absorption and first pass metabolism) were applied to dosing where subjects held the solution sublingually for 7 minutes and then swallowed the remaining solution. Without any additional fitting, the model was able to correctly predict the final Cp-time profile. This suggests that the assumption of high metabolism in the oral mucosa was correct.



Conclusions:

Sublingual dosage forms are usually developed to combat problems of standard oral dosage forms – late onset of action and/or high first pass extraction. This would not be the case for nifedipine where the standard PO solution results in a faster onset of action as well as higher bioavailability. Nifedipine seems to have low sublingual absorption and undergoes significant first pass metabolism in the oral mucosa. The final calibrated model was able to correctly predict the sublingual administration with swallowing of unabsorbed amount after 7 minutes with respect to lower bioavailability (~70%), lower Cmax (~200ng/mL) and delayed Tmax (~1hr) when compared to a PO solution dose (Fb ~73%, Cmax ~130ng/mL and Tmax 45 minutes).

References

1. Rodgers T., J Pharm Sci 2007, 96(11): 3151-3152
2. Rodgers T., J Pharm Sci 2007, 96(11): 3153-3154
3. Palma, J.A., Archiv Invest Med 1989, 20:120-135
4. Patki, K.C., Drug Metab Dispos 2003, 31:938-944
5. Zhang Q.Y., Drug Metab Dispos 2007, 35(9):1617-23
6. Iwao T., Drug Metab Pharmacokinet 2002, 17(6): 546-53
7. van Harten J., Lancet 1987, 1363-1364
8. Patki K.C., Drug Metab Dispos 2003, 31:938-944
9. Inoue S., Xenobiotica 2006, 36(6): 499-513

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