Supersaturation Properties of Poorly Soluble Weak Bases are Key Factors in Determining Oral Drug Absorption: A Simulation Study of Nifedipine Using the ADAM Model (Simcyp v7.1)

D. Turner[1], M. Jamei[1], G. T. Tucker[1,2], and A. Rostami-Hodjegan[1,2]

d.turner@simcyp.com

1- Simcyp Ltd, Blades Enterprise Centre, John St, Sheffield, S2 4SU, UK
2- Academic Unit of Clinical Pharmacology, University of Sheffield, Sheffield, UK

Objectives

(1) To assess assumptions about the supersaturation properties of nifedipine (NIF), as a model poorly soluble, weakly basic drug, when *predicting* oral absorption from immediate release (IR) solid dosage forms.

(2) To model the extent of inter-individual variability in the predicted fraction absorbed into the enterocytes (fa) in a virtual, healthy North European population.

Solubility and Supersaturation

Drug solubility can be measured at thermodynamic equilibrium or when the solution is supersaturated (kinetic solubility). The onset of supersaturation may be followed by either immediate or gradual precipitation [1,2]. The ability to form supersaturated solutions and the rate of precipitation is drug- and medium-specific and cannot be predicted easily [1]. Therefore, in the absence of experimental data, assumptions regarding these properties may critically affect simulation of absorption from *in vitro* data and the prediction of oral bioavailability.

Poorly soluble weak bases are expected to have a greater extent of ionisation and hence a higher solubility in the acidic milieu of the fasted-state human stomach. Thus, dissolution from an IR formulation of such a drug may be partial or complete in the gastric contents, but precipitation may occur upon entering the duodenum. Accordingly, the ability to supersaturate and the kinetics of equilibration can significantly affect the rate and/or extent of oral absorption [2].

Nifedipine: A Case Study

The Advanced Dissolution, Absorption, and Metabolism (ADAM) model [3], implemented within Simcyp v7.1 (www.simcyp.com), was used to simulate the absorption of the BCS Class 2 compound NIF (pKa 2.8). NIF is poorly soluble in aqueous buffer (0.011 mg/mL, pH 6.5 [4]), but has enhanced solubility in the human stomach due to increased ionisation. Because of its low pKa the extent of ionisation of NIF and, therefore, this solubility enhancement is pH-dependent. The consequences of variability in gastric pH on the dose number (Do) of NIF are summarised in Table 1: Do = (Dose / Volume of fluid with Dose) / Solubility.

Table 1: Dose Numbers (Do) of NIF at different gastric pH values (population 10th, 50th & 90th percentiles) and volumes of fluid intake. A Do value of > 1 indicates incomplete solubility in gastric fluid.

	Volume of Fluid taken with Dose					
	125 mL			**250 mL**		
Dose (mg)	pH 1.0	1.5	2.2	pH 1.0	1.5	2.2
10	0.1	0.2	**1.0**	0.1	0.1	0.6
90	0.7	**2.1**	**8.6**	0.4	**1.3**	**5.0**

NIF can form supersaturated solutions [5,6], but the rate of precipitation from such solutions does not appear to have been reported. Variability in the oral bioavailability of NIF is unlikely to be related to permeability ($P_{eff,man}$ from Caco-2 data = 7×10^{-4} cm.s^{-1}).

ADAM Simulations

NIF absorption was simulated for 4 doses in the range 10 to 90 mg, 9 particle sizes from 0.1 µm to 200 µm, and variable fluid intake (125 mL and the BCS standard volume of 250 mL). The first-order precipitation rate constant (PRC) was varied from 0.04 to 400 h^{-1}. Simulations were run for a representative healthy, male North European Caucasian as well as a virtual population of 100 such individuals.

Absorption of NIF was assumed to occur throughout the small intestine and in the colon [7]. Simulations covered a period of 72h after dosage, thereby allowing for full gastrointestinal transit. At this stage of the development of the algorithms, inter-individual variability in gastric pH was not simulated. Aqueous solubility was used since data on solubility in biorelevant media were not available.

Results

The predicted value of fa was found to be sensitive to dose, particle size, volume of fluid taken with the dose and the precipitation rate constant. For example, in a representative healthy, male North European Caucasian, fa ranged from 0.14 to 1.0 for a 90 mg dose and 250 mL of fluid intake (Fig. 1).

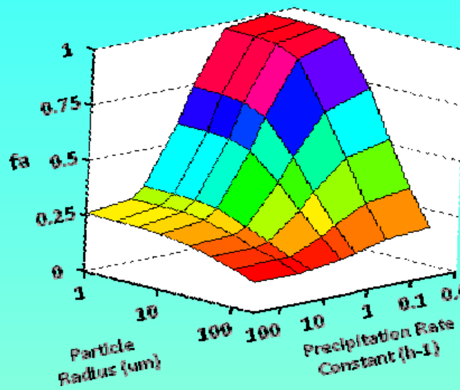

Figure 1: Predicted fa *vs.* particle size and precipitation rate from supersaturated solution for a 90 mg dose of NIF taken with 250 mL fluid. The simulations were run for a representative healthy, male North European Caucasian.

Considerable variation in predicted fa was also found as a function of both particle size and precipitation rate (Fig. 1). This variability was noted for all particle sizes tested, but was greatest at the smallest values (0.1 and 1 µm). Average fa in the virtual population was found to be sensitive to PRC, and inter-subject variability was greatest with rapid precipitation from supersaturated solution (*i.e.,* at low fa) (Fig. 2).

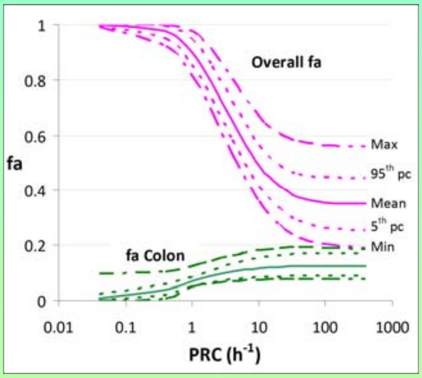

Figure 2: Predicted net fa of NIF in 100 virtual individuals *vs.* precipitation rate constant (PRC) (Max, Min, 5th & 95th pc, and Mean refer to the population maximum and minimum, 5th and 95th percentile, and mean fa values, respectively). The fraction absorbed from the colon and its variability is shown in green. Dose = 90 mg; intake fluid volume = 250 mL fluid; particle radius = 1 µm.

An increase in colonic absorption (green line, Figure 2) partially compensated for decreased absorption in the small intestine and, in some individuals, was predicted to account for most of the overall fa value when precipitation was rapid.

Conclusions

The ADAM simulations demonstrate that the prediction of the oral absorption of poorly soluble weak bases from IR preparations is likely to depend critically on assumptions about supersaturation properties with respect to the interplay of factors including dose, particle size, and the volume of fluid intake. They also illustrate how inter-individual variability in physiological factors contributes to variability in the oral absorption of NIF.

References

1. Box KJ *et al.* (2006) *J Pharm Sci* **95**:1298; **2.** Kostewicz ES *et al.* (2004) *J Pharm Pharmacol* **56**; **3.** Jamei *et al.* (2007) Poster No. 14 at the Current Meeting; **4.** Sutton *et al.* (2006) *Pharm Res* 23 1554; **5.** Suzuki *et al.* (2001) *Drug Dev Ind Pharm* **27**:951; **6.** Cilurzo *et al.* (2007) *Eur J Pharmaceut Biopharmaceut*. in press; **7.** Bode *et al.* (1996) *Eur J Clin Pharmacol* 50:195.