Modeling of Cilostazol absorption and pharmacokinetics in Beagle Dogs and design of *in-vitro* dissolution experiment to model the *in-vivo* absorption

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Abstract

Purpose: The purpose of this study was to evaluate the *in-vitro/in-vivo* (IVIV) correlation for a Class II compound and to design an *in-vitro* dissolution experiment that improves this IVIV correlation by taking into account the sink created by the removal of dissolved drug from the intestinal lumen due to high permeability.

Methods: GastroPlus™ (Simulations Plus, Inc.) was used to construct a model describing the *in-vivo* dissolution, absorption, and distribution of the poorly soluble drug Cilostazol, including the particle size distribution of the administered formulation. The plasma concentration-time (Cp-time) profiles in dogs for two formulations with different particle size distributions were simulated utilizing the built-in dissolution model (based on particle size distribution and the drug's pH-dependent solubility) as well as the *in-vitro* dissolution profile measured in FaSSIF media. Observed absorption and plasma concentration profiles were used to fit the *in-vivo* dissolution profile for both formulations and these profiles were compared with the *in-vitro* dissolution profiles. DDDPlus™ (Simulations Plus, Inc.) was then used to design a multi-phase *in-vitro* dissolution experiment to obtain an *in-vitro* dissolution profile corresponding to the desired *in-vivo* profile.

Results: Using the built-in dissolution model (utilizing the particle size distribution and the drug's solubility), the Cp-time profile measured in beagle dogs was closely reproduced for two different particle size distributions, while using the *in-vitro* measured dissolution profile grossly overestimated the plasma concentrations caused by fast initial dissolution that quickly reached solubility limit. The poor agreement between *in-vitro* and *in-vivo* dissolution profiles was caused by the inability of a simple *in-vitro* dissolution experiment (with a much smaller dose) to reproduce slow and nearly linear *in-vivo* dissolution caused by the fact that permeability becomes the rate limiting step *in vivo. In vivo,* the low solubility ceiling only allows a small amount of drug to dissolve until the permeability sink removes some of the drug at a rate slower than observed *in vitro.* A new, multi-phase, *in-vitro* dissolution experiment was designed to model these permeability-rate-limited sink conditions and produce an *in-vitro* profile that could be used to simulate *in-vivo* dissolution.

Conclusions: The study showed the importance of careful design of *in vitro* dissolution experiments for Class II compounds. For these compounds, *in vivo* dissolution is not only affected by the particle size and overall solubility of the drug, but also by the permeability, which creates sink conditions in the gastrointestinal tract, thus promoting more drug to dissolve.

Data

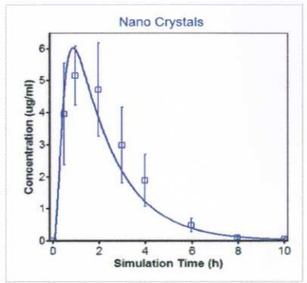
The study was conducted using literature data for *in vitro* dissolution profiles of three Cilostazol formulations (Nano Crystals – particles 0.1 to 0.4 um, Jet Milled – particles 0.3 to 13.7 um, and Hammer Milled – particles 0.3 to 122 um) in water, FaSSIF and FeSSIF media [1], as well as plasma concentration – time profiles after oral administration of Cilostazol to beagle dogs [1,2]. Drug properties were obtained from ADMETPredictor™ (pKa, Peff, Dw, Fup) or used directly as reported [1] in literature (logD, solubility).

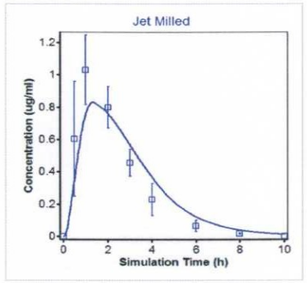
References

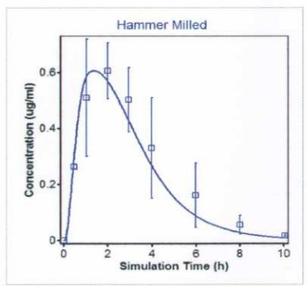
- Jinno, J.; et al. Effect of particle size reduction on dissolution and oral absorption of a poorly water-soluble drug, Cilostazol, in beagle dogs. *Journal of Controlled Release* 2006, **111:** 56-64
- Akiyama, H; et al. The absorption, distribution and excretion of a new antithrombotic and vasodilating agent, Cilostazol, in rat, rabbit, dog and man. *Arzneimittelforschung* 1985, **35:** 1124-32

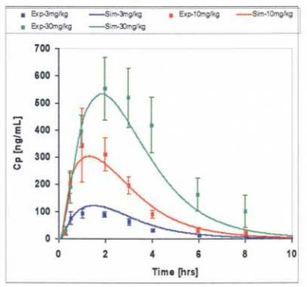
Methods

• GastroPlus was used to fit the model for prediction of Cp-time profiles [1] of the three Cilostazol formulations (dose of 100mg/body) employing a dissolution model where the drug dissolution is a function of solubility and particle size distributions. The fitted Absorption-PK model was validated by comparison of simulated profiles for three different dose levels with measured plasma-concentration time profiles of another Cilostazol formulation [2]. Fitted values for Clearance (0.617 L/h/kg) and Volume of Distribution (1.048 L/kg) were close to literature values [1] obtained from the Cp-time profile for IV administration (CL=0.6 L/h/kg, Vd=0.72 L/kg).



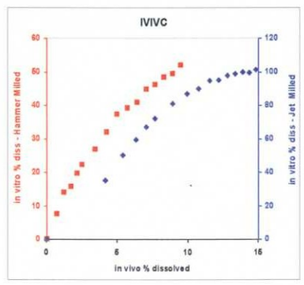






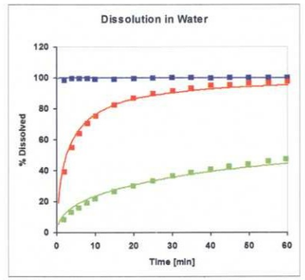
In each graph, points represent experimental values, lines show simulated profiles

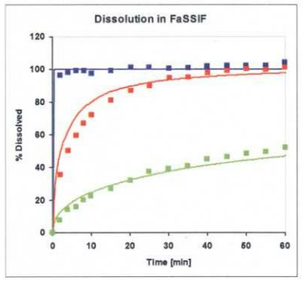
2. The fitted Absorption-PK model was coupled with the *in vitro* dissolution profiles for the three formulations with varying particle sizes. Simulated Cp-time profiles for Jet Milled and Hammer Milled formulations were fitted to the experimental data by optimizing their dissolution profiles. Obtained *in vivo* dissolution profiles were compared with the experimental *in vitro* dissolution profiles.

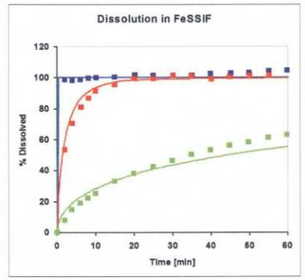


3. DDDPlus™ was used to design *in vitro* dissolution experiments to replicate the fitted *in vivo* dissolution profiles.

First the ability of the model to reproduce the *in vitro* dissolution of Cilostazol in water, FaSSIF and FeSSIF media was verified. As shown on the figures, there was an excellent match between simulated (solid lines) and experimental (squares) profiles for Nano Crystals (blue), Jet Milled particles (red) and Hammer Milled particles (green) in all three media.







4. For the Class II compound, with low solubility and high permeability, the absorption of the drug is normally limited by its dissolution. However, due to the low solubility, dissolution *in vivo* was limited by the permeability sink. To model this situation, a multi-phase experiment was designed with gradually increasing volume of dissolution media. The volume increase *in vitro* will model the decrease of dissolved drug concentration due to drug absorption *in vivo.*