Designing *In Vitro* Dissolution Tests to Better Mimic *In Vivo* Release

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In vitro dissolution tests were traditionally designed for quality control. USP methods commonly used to evaluate the release rate of new controlled release dosage forms are often based on such experiments. The need to design a new *in vitro* experiment arises when a suitable *in vitro – in vivo* correlation cannot be obtained because *in vivo* release is significantly different from *in vitro* experiments. Modern simulation methodology offers new solutions to this problem. The application of state-of-the-art simulation methods for the numerical deconvolution of *in vivo* release profiles is combined with simulation software for the detailed mechanistic simulation of *in vitro* dissolution experiments to produce a method for optimizing *in vitro* experimental conditions (instrument speed, pH, and fluid volume) as functions of time in order to replicate deconvoluted *in vivo* release behaviors.

Methods:

1. GastroPlus™ [Simulations Plus, Lancaster, CA] was used to fit the *in vivo* absorption and metabolism models for Cp-time profiles of three Cilostazol formulations (nano-crystal, jet-milled,and hammer-milled) employing the built-in dissolution model, where the drug dissolution is a function of solubility and particle size distributions. Fitted parameters were Vmax and Km for 3A4 metabolism, colon absorption scale factor, and mean precipitation time.

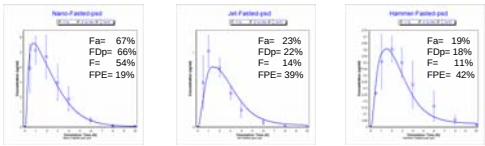

Figure 1. Predicted and observed plasma concentration-time profiles for the three 100 mg solid Cilostazol formulations in dog with built-in dissolution model and fitted CYP 3A4 Vmax and Km, colon absorption scale factor, and mean precipitation time. Relative distribution of 3A4 in gut for beagle dog was assumed to be similar to human.

2. Cp-time was then predicted using the fitted absorption-PK model coupled with the *in vitro* dissolution profile for each of the formulations.

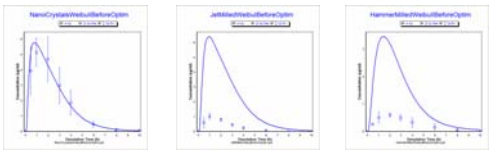

Figure 2. Predicted and observed plasma concentration-time profiles for the three 100 mg solid Cilostazol formulations in dog with fitted absorption/PK model from Figure 1, but using the *in vitro* dissolution profile from literature for each formulation as the *in vivo* release rate. The *in vitro* dissolution profile only provides a reasonable prediction for the nano-crystal formulation.

3. In vivo dissolution-time profiles were then fitted to the Cp-time data for each formulation, assuming that the absorption/PK model obtained in step 1 was adequate. The ("deconvoluted") *in vivo* dissolution profiles so obtained for the 100 mg doses were then compared with the *in vitro* dissolution profiles for 5 mg (no 100 mg data were available).

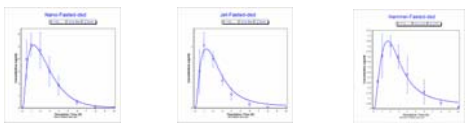

Figure 3. Predicted and observed plasma concentration-time profiles for the three 100 mg solid Cilostazol formulations in dog utilizing absorption/PK model from Figure 1, with fitted ("deconvoluted") *in vivo* dissolution profiles using two Weibull function parameters for each formulation.

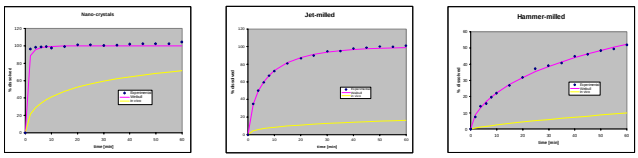

Figure 4. Comparison of "deconvoluted" *in vivo* and *in vitro* dissolution profiles for nano-crystal, jet-milled and hammer-milled formulations. The deconvoluted *in vivo* release rate is slower than the original *in vitro* experiment for all formulations. Note: *in vitro* data were for 5 mg cilostazol, while *in vivo* data are for 100 mg.

Reference:

1. Jinno, Jun-ichi; 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

Data:

In vitro dissolution profiles for three Cilostazol formulations (nano crystals (particles 0.1 to 0.4 µm), jet-milled (particles 0.3 to 13.7 µm), and hammer-milled (particles 0.3 to 122 µm) in water, FaSSIF and FeSSIF media, as well as plasma concentration–time profiles after oral administration of the same three Cilostazol formulations to beagle dogs in fasted and fed states were obtained from literature [1]. Drug properties and pharmacokinetic parameters were obtained from ADMET Predictor [Simulations Plus, Lancaster, CA] (pKa, Peff, Dw, Fup) or used directly as reported in literature [1] (logD, solubility, CL, Vd)

4. DDDPlus™ [Simulations Plus, Lancaster, CA] was used to design *in vitro* dissolution experiments to replicate the desired *in vivo* dissolution profiles. First, the ability of the DDDPlus model to reproduce the *in vitro* dissolution of the three different Cilostazol formulations in FaSSIF media was verified. These simulations allowed calibration of the phosphatidylcholine surfactant effect parameter for increased solubility within DDDPlus, for which the same value is used in all three simulations.

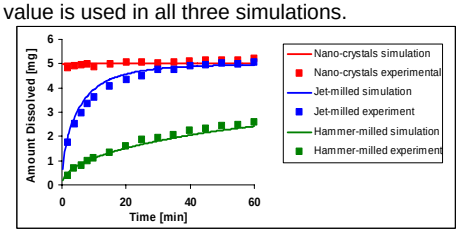

Figure 5. Simulated *in vitro* dissolution profiles for nano-crystals, jet-milled, and hammer-milled formulations. A single value for the Surfactant Effect parameter was fitted across all three data sets.

For Class II compounds (low solubility and high permeability), absorption is primarily limited by dissolution. However, due to high permeability, dissolved drug is quickly removed from the gut lumen by absorption, allowing more drug to dissolve ("sink effect"). To model this situation, a multi-phase experiment was designed with gradually increasing volume of dissolution media. The volume increase *in vitro* emulates the decrease of dissolved drug concentration due to drug absorption *in vivo.*

Table 1. Multi-phase *in vitro* dissolution experiment designed to model the *in vivo* dissolution. 100mg of drug is being dissolved in FaSSIF media in USP 2 apparatus (paddle) with stirring speed 50rpm

Time, min.	Fluid Volume, mL Jet-milled	Fluid Volume, mL Hammer-milled
0	560	45
30	720	75
60	840	105
90	930	135
120	1050	175
180	1170	215
240	1250	255
300	1330	295
360 . . . 540	1410 . . . 1530	335 . . . 405
600	1590	440

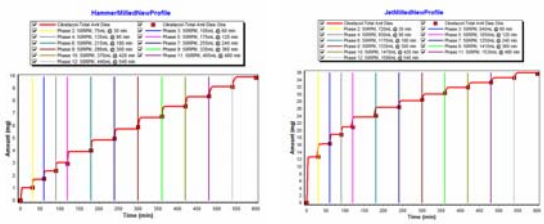

Figure 6. *In vivo* dissolution profile for hammer-milled and jet-milled formulations (squares) and the dissolution simulated by multi-phase experiments (solid lines). The discontinuities in simulated profiles are caused by using step volume increases in DDDPlus at each observed time point.