Research Article

Theme: Facilitating Oral Product Development and Reducing Regulatory Burden through Novel Approaches to Assess Bioavailability/Bioequivalence

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A Technique to Estimate *In Vivo* Dissolution Profiles Without Data from a Solution

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Abstract. Dissolution tests are expected to ensure adequate *in vivo* product performance. Given the recent progress in the ability to predict of human permeability, it is possible to synthesize the plasma drug concentration–time profile from human permeability predictions and the results of the first-in-human trial and use these data to synthesize a pharmacokinetic profile for a solution and provide an initial estimate of the *in vivo* dissolution profile. This manuscript provides details of such a deconvolution methodology in order to provide an initial estimate of *in vivo* dissolution. Plasma metoprolol concentration–time data from a previously published study examining the pharmacokinetics of three metoprolol formulations (100 mg), slow, moderate, and fast releasing, and an oral solution (50 mg) were used to estimate *in vitro* dissolution profiles. A one-compartment unit impulse function was used, and the absorption rate was estimated from animal permeability data (synthetic solution method). The results were compared to those obtained using a unit impulse function estimated from the oral solution data. *In vivo* dissolution profiles estimated from animal permeability data were similar to those estimated from the oral solution data. Ratios of absorption rate constants (synthetic solution method/oral solution) ranged from 1 to 1.3. The synthetic solution method offers a way to estimate *in vivo* dissolution profile through deconvolution. It is applicable in cases where it is not possible or feasible to obtain data from a solution. It performs best in cases where dissolution is the rate-limiting step in the absorption process.

KEY WORDS: dissolution; *in vitro/in vivo* correlation; permeability.

INTRODUCTION

Regulatory agencies are encouraging pharmaceutical companies to employ a quality by design paradigm (QbD) when developing formulations and manufacturing processes (1). A key objective of a QbD paradigm is to identify critical quality attributes (CQAs) which are physical, chemical, biological, or microbiological properties or characteristics that must be controlled directly or indirectly to ensure that product quality assures the expected safety and efficacy for patients. Once a CQA is identified, a further hurdle in implantation of QbD is the establishment of the relation between the CQAs and safety and efficacy is identified. Given the multiple number of potential attributes, it is not financially feasible to try to identify CQAs and then establish relationships in clinical trials of safety and efficacy. Thus a surrogate that can be linked to *in vivo* product performance needs to be established with the properties that the surrogate offers substantial savings of time and money. Further, there is a need to start determining CQAs early in the

development of a compound as this often represents a time where product attributes are most variable and thus offer the most opportunity to examine their impact.

Dissolution testing is often used as a surrogate to ensure quality (2). For poorly soluble compounds (BCS classes II and IV) and modified release formulations, dissolution is the rate-limiting step in the absorption process. Consequently, the dissolution tests are expected to ensure adequate *in vivo* product performance. These tests are typically developed around the time that human studies are initiated. Often the tests do not take into consideration the *in vivo* product performance and are optimized for analytical throughput. The first-in-man study represents the first opportunity to characterize *in vivo* performance and use these results to facilitate development of appropriate dissolution methods. However, the lack of a solution, either because of resource constraints or compound solubility, can preclude the use of traditional deconvolution techniques to assess *in vivo* dissolution. Given the recent progress in the ability to predict human permeability, it is possible to synthesize the plasma drug concentration–time profile from human permeability predictions and the results of the first-in-human trial, and to use these data to synthesize a pharmacokinetic profile for a solution and provide an initial estimate of the *in vivo* dissolution profile. Thus it is possible to estimate the *in vivo*

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dissolution profile of a compound around the time that dissolution methodologies are developed. The *in vivo* dissolution profile can then be used to develop an *in vitro* methodology that will likely be more reflective of what happens *in vivo*. This manuscript provides details of such a deconvolution methodology in order to provide an initial estimate of *in vivo* dissolution.

EXPERIMENTAL SECTION

Clinical Study

Plasma metoprolol concentration–time data from a previously published study examining the pharmacokinetics of three metoprolol formulations (100 mg), slow, moderate, and fast releasing, and an oral solution (50 mg) were used to estimate *in vivo* dissolution profiles (3). This study had several attributes that made it attractive for evaluation of this methodology: it utilized sustained release formulations that would assure dissolution would be a rate-limiting effect, and it included a solution that allowed comparison of this methodology with that using a solution and the authors developed an *in vitro*–*in vivo* correlation IVIVC from the data which allowed comparison of the predicted *in vivo* dissolution profile with the dissolution profile from the *in vitro* method.

Briefly, seven healthy volunteers received single oral doses in a randomized crossover fashion. Serial blood samples were collected over 48 h and analyzed by a validated HPLC assay using fluorescence detection.

In Vivo Dissolution Assessment

Plasma metoprolol concentration–time profiles after oral administration of solid formulations are a function of *in vivo* dissolution, absorption, distribution, and elimination. Profiles obtained after oral administration of a solution are a function of the same functions with the exception of *in vivo* dissolution as the drug is already dissolved. The pharmacokinetic profile of the solution can be deconvolved from that of a solid formulation to derive the *in vivo* dissolution profile. Thus, *in vivo* dissolution profiles for each individual after each solid formulation in the pharmacokinetic dataset were obtained using deconvolution through a convolution method as implemented in WinNonlin™ (WinNonlin Enterprise Version 5.2 with IVIVC Toolkit; Pharsight Corporation, Mountain View, CA) using the automatic smoothing and initial rate not constrained to be zero options.

Deconvolution by this method requires a compartmental model that describes the plasma drug concentration–time profile for a solution and is called a unit impulse function. Two methods were utilized to obtain the unit impulse function. The first, hence noted as the synthetic method as it synthesizes the unit impulse for a solution, involved estimation of a unit impulse function without using data obtained following administration of a solution. The unit impulse function took the following form:

$$UI_{i,t} = e^{\lambda z_i t} - e^{K_a t} \quad (1)$$

where $UI_{i,t}$ is the unit impulse function for subject i at time t , λz_i is the elimination rate constant for subject i , and K_a the

absorption rate constant. K_a was assumed to be constant (1.22 h^{-1}) for all individuals and estimated from the following equation:

$$K_a = 2 \cdot \frac{P_{\text{eff}}}{R} \quad (2)$$

where P_{eff} is the effective human permeability of metoprolol and R is the radius of the intestine. P_{eff} was estimated from Caco-2 permeability data ($18.8 \times 10^{-6} \text{ cm/s}$) (4) using a correlation between Caco-2 permeability at pH 6.5 and human jejunum permeability developed by previous investigators (all drug correlation) (5). A value of 1 cm was used for R (6). An individual subject's λz_i value was estimated from the terminal phase of the pharmacokinetic profile following administration of the solution, since the controlled release properties of the other formulations influenced the associated terminal elimination phase. It is suggested that in most cases the terminal phase will reflect elimination. When a controlled release formulation is developed, data from immediate release formulations are typically available. In cases where data are not available to estimate the elimination rate (e.g., immediate release product with “flip-flop” or absorption rate-limited pharmacokinetics), human half-life may be estimated from rat pharmacokinetic data (7). The second unit impulse function (modeled solution) was obtained by fitting a one-compartment model with first-order absorption to each individual's solution data, thus K_a and λz differed for each individual subject. Deconvolution using the modeled solution data as the unit input response was considered the reference method.

Output from the deconvolution included fractional (fraction of dose) and cumulative (scaled amount based on unit impulse function) input rates estimated at 0.2-h intervals from 0 to 20 h. The fractional input rate–time profile was considered the *in vivo* dissolution profile. A simple first-order dissolution model was fit to *in vivo* dissolution–time data for each subject and formulation:

$$\% \text{Dissolved} = 1 - e^{-K_d * (t - t_{\text{lag}})} \quad (3)$$

where K_d is the *in vivo* dissolution rate, t_{lag} is the lag time in dissolution, and t is time. Percent dissolved values of zero were omitted from each data set. Modeling was conducted using WinNonlin.

RESULTS

In Vivo Dissolution Assessment

Mean *in vivo* dissolution profiles for both methods are shown in Fig. 1, and dissolution rates are compared in Table I. A comparison of individual subject's fractional input values at corresponding time points is shown in Fig. 2. Mean t_{lag} values ranged from 1 to 11 min and did not appear to be influenced by the dissolution rate.

DISCUSSION

The results from deconvolution using the synthetic unit impulse function were in good agreement with those derived

Fig. 1. Mean *in vivo* metoprolol dissolution-time profiles obtained using modeled solution (blue lines) or synthetic unit impulse function (red lines) on data derived following oral administration of three different metoprolol controlled release formulations

using the modeled solution. Ratios of the first-order dissolution rates ranged from 1.0 to 1.3. It is acknowledged that the performance of the synthetic method is dependent on how closely the unit impulse function represents that of a solution. In this instance elimination rate values could be individualized. The mean absorption rate estimated from animal data was nearly identical to that resulting from the modeling of the solution. To assess the sensitivity of the synthetic method to the estimate of K_a , the data were also analyzed using an input function where the mean K_a value was twice and one half that of the original value. When K_a was twice that of the original estimate, estimated K_d values ranged from 10 % lower for the slow formulation to 27 % lower for the fast formulation relative to their respective original values. On the other hand, when the K_a was half that of the original estimate, K_d values ranged from 73 % higher for the slow formulation to 222 % higher for the fast formulation relative to their respective original values. Thus the more dissolution limited a compound is (large true K_p/K_d ratio), the less sensitive it is to errors in K_a measurements. Additionally, when the estimate of K_a was half of that of the original value, the K_p/K_d ratios of all formulations went from those indicating a dissolution-limited system (values >1) to ratios indicating a permeability-limited system (values <1). It is therefore not surprising that the method is sensitive to cases where there is such a fundamental error.

It should also be noted that the present example utilized a simple one-compartment disposition model. More complex disposition models could be utilized. A recent study found

Table I. Comparison of *In Vivo* Absorption and Dissolution Rates for Three Metoprolol Controlled Release Formulations

Parameter	Geometric mean (%CV) value by unit input function	
	Synthetic	Solution
K_a (h^{-1})	1.22 (fixed)	1.21 (57.1)
K_d for fast formulation (h^{-1})	1.07 (41.1)	1.06 (161)
K_d for medium formulation (h^{-1})	0.529 (16.7)	0.408 (22.9)
K_d for slow formulation (h^{-1})	0.346 (42.3)	0.288 (38.2)

Fig. 2. Comparison of fractional input values following deconvolution using solution and synthetic unit impulse functions (UIR) of data derived following oral administration of three different metoprolol controlled release formulations. Thin lines represent values for individual subjects and formulations. The thick line is the line of unity

that physiologically based pharmacokinetic models (PBPK) were able to accurately predict the multiphasic shape of the pharmacokinetic profiles for many of the compounds tested (8). Since it is the shape of the unit input function that is most important (rather than the magnitude on the absorption axis), a PBPK simulated solution unit impulse might offer advantages over one derived from a one-compartment model when a more complex disposition is anticipated.

The investigators who ran the clinical trial in this study also developed an IVIVC (3). Four dissolution test conditions were developed, and correlations were examined between the fraction remaining to be dissolved in the *in vitro* system with the fraction remaining to be absorbed derived from the *in vivo* data. The best method (highest correlation) involved apparatus I with a rotation speed of 150 rpm and at a pH of 6.8. The investigators were able to develop and IVIVC that met the acceptance criteria acceptable according to the FDA's guidance (9). The mean *in vitro* dissolution profile of the three solid oral formulations used in the clinical trial is

Fig. 3. Comparison of *in vitro* (red lines) and estimated *in vivo* (blue lines) dissolution profiles for three different metoprolol controlled release formulations. *In vitro* used apparatus I, pH 6.8, 150 rpm as reported in (9). The *in vivo* profile was estimated using the synthetic solution method

compared with the *in vivo* dissolution profile derived using the synthetic method in Fig. 3. The *in vitro* and *in vivo* dissolution profiles are very similar; F2 test comparisons ranged from 23 to 42 indicating that average differences were between 3 and 7 %. This suggests that estimation of the *in vivo* dissolution profile may greatly facilitate IVIVC development.

CONCLUSION

The synthetic solution method offers a way to estimate *in vivo* dissolution profile through deconvolution. It is applicable in cases where it is not possible or feasible to obtain data from a solution. It performs best in cases where dissolution is the rate-limiting step in the absorption process.

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