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In Vitro Dissolution: Current Issues and in Vivo Relevance.

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Recent regulatory guidance in the last 10 years allows dissolution to serve as a surrogate for in vivo bioequivalence studies in certain circumstances (e.g. BCS, SUPAC). Nevertheless, dissolution issues remain, such as for "problem drug substances" and "complex" formulations. The objectives of this presentation are (a) to discuss challenges of the in vitro dissolution test and (b) to summarize two approaches to relate in vitro dissolution data to in vivo pharmacokinetic profiles.

Although the historical value of in vitro dissolution is positive and although in vitro dissolution can now serve as a surrogate for in vivo bioequivalence, the in vitro dissolution test presents many potential challenges. Decades of efforts have not lead to a universal dissolution medium. A universal dissolution media has not emerged and remains elusive. In spite of an understanding of the composition within the gastrointestinal lumen and related biopharmaceutics, this situation where no single in vitro medium has evolved would appear to reflect that in vitro dissolution is product-specific. Theophylline extended-release (ER) capsules is an example supporting that in vitro dissolution is product-specific. In the USP, there are 10 different compendial dissolution test for theophylline ER capsules. Interestingly, two products employ the same test method and media, and are clinically doses every 12 hours. However, their in vitro release specifications are very different: one product requires 85%-115% dissolved in vitro at 5 hour, while the other requires 50-80% dissolved in vitro at 5 hour. The implications of in vitro dissolution being product-specific are significant, including the need to design human in vivo studies in a development program, to support in vitro dissolution test validation.

While product-specific dissolution reflects the real complexity of drug release from a dosage form, it would appear that other "complexities" of in vitro dissolution are false expectations, or

hopes, that may not be realistic. For example, general expectations for in vitro dissolution often include (a) complete release and (b) identical profiles [or at least identical specifications] across all dosage strengths. These general expectations are most frequently held, even when (a) release is incomplete in vivo or (b) sink-conditions do not prevail for higher doses. Of course, in vivo relevance of the in vitro test is hoped for, even when these expectations are forced upon the in vitro test. For example, a solution to lack of sink-conditions for higher doses is addition of surfactant, even if such addition leads to the in vitro test becoming less discriminating.

The second objective of this presentation is to summarize two approaches to relate in vitro dissolution data to in vivo pharmacokinetic profiles. The two approaches are denoted Deconvolution IVIVC and Convolution IVIVC, respectively. The first approach is denoted Deconvolution IVIVC and emphasizes an interest in understanding the kinetics of drug absorption, including the kinetic role of dissolution in overall oral drug absorption kinetics. A model to carryout Deconvolution IVIVC is:

$$F_a = \frac{1}{f_a}\left(1 - \frac{\alpha}{\alpha - 1}\left(1 - F_d\right) + \frac{1}{\alpha - 1}\left(1 - F_d\right)^{\alpha}\right)$$

where F_a is the fraction of the total amount of drug absorbed at time t, f_a is the fraction of the dose absorbed at $t = \infty$, α is the ratio of the apparent first-order permeation rate constant (k_p^{app}) to the first-order dissolution rate constant (k_d), and F_d is the fraction of drug dose dissolved at time t (1). Figure 1 illustrates equation 1 for a varying range of alpha values. This approach represents a mechanistic approach to elucidate the kinetic importance of dissolution and can be performed in early formulation development (e.g. even with only one formulation that has both in vitro and in vivo data). Case studies will include formulations of drugs of various BCS classes (e.g. BCS class 1, 2, and 3), exemplifying the role of drug biopharmaceutic properties (e.g. solubility, permeability) and formulation properties on product performance. Additionally, implications for a) the use of intestinal permeability data (e.g. Caco-2) and dissolution data during product development and b) the estimation of dissolution specifications in early product from biopharmaceutic data and will be emphasized.

Convolution IVIVC is a second approach and is exemplified by the FDA Level A correlation approach. In the FDA "Guidance for Industry Extended Release Oral Dosage Forms: Development. Evaluation, and Application of In Vitro/In Vivo Correlations", FDA Level A correlation is defined to be a predictive mathematical model for the relationship between the entire in vitro dissolution/release time course and the entire in vivo response time course, e.g. the time course of plasma drug concentration or amount of drug absorbed. In contrast to the Deconvolution IVIVC approach, this approach focuses on plasma profiles themselves, and well as issues concerning plasma profiles (e.g. the bioequivalence question). Hence, Convolution IVIVC has utility in late

product development when regulatory issues are a focus. An example of the FDA Level A correlation approach will be discussed.

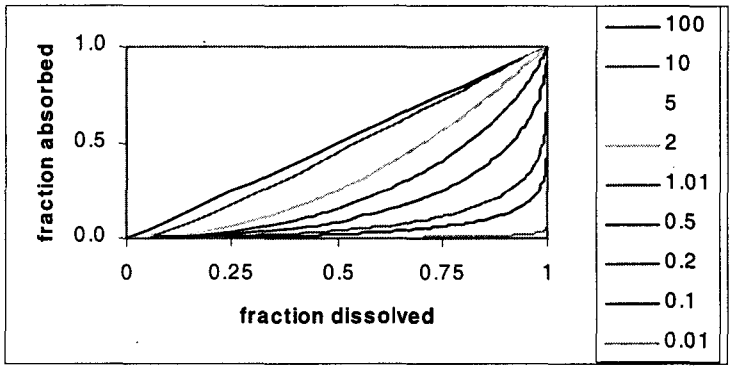

Figure 1. Family of curves for $f_a = 1$. The theoretical relationship between F_a and F_d is illustrated for a range of alpha values. Generally, a greater fraction of dose dissolved yields a greater fraction of total amount of drug absorbed. For low values of alpha, where permeation is rate-limiting, the relationship between F_a and F_d is highly non-linear.

REFERENCES

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