It is natural to try to relate in vitro dissolution data to in vivo pharmacokinetic data. An effort to connect dissolution and pharmacokinetic results is often referred to as "in vitro-in vivo correlation" (IVIVC) analysis. Over the last 40 years, three often-used approaches to perform IVIVC are the so-called Level A, Level B, and Level C approaches. Among these three, Level A is generally viewed as the best method, since Level A utilizes all dissolution and pharmacokinetic data. Level B also utilizes all dissolution and pharmacokinetic data, but arguably is less insightful and helpful.

**Level A IVIVC and its Failure for Immediate Release**

For Level A analysis, the fraction drug absorbed (Fa) is plotted against the fraction drug dissolved (Fd). The fraction drug absorbed profile is obtained by deconvoluting the plasma profile. Deconvolution is essentially a back calculation to answer the question: "What must the drug absorption profile have been, given the plasma profile?"

Of course, deconvolution requires some assumptions. The often sought out Level A profile is a one-to-one relationship between absorption and dissolution, with slope equal to one and y-intercept of zero. Figure 1 presents a practically ideal Level A result.

![Fig 1](http://dissolutiontech.com/DTresour/800Articles/800_art1.html)

**Figure 1.** Fa versus Fd profile for diltiazem HCl ER capsules. Release is rate-limiting, resulting in a linear profile (i.e. Level A IVIVC).

So why has the relationship in Figure 1 been a Holy Grail over the last 30 years? The simple answer lies in the fact that alternative methods are more difficult, and were practically unavailable 30 years ago. Level A analysis requires linear regression of Fa against Fd. Linear regression was (and still can be) easily performed by hand. The first commercially available computers provided linear regression software. Hence, given its advantages over Level B and Level C, along with the computational availability to perform linear regression, Level A analysis had become the preferred method to relate in vitro dissolution to in vivo pharmacokinetics.

A statistic from Level A analysis is $r$, the correlation coefficient. Its square, $r^2$, ranges from zero to one and is a measure of the strength of relationship between Fa against Fd. Often, results with sufficiently large $r^2$ (e.g. greater...
than 0.9) yielded "a (successful) correlation." An r2 value that was too low resulted in a "no correlation" conclusion.

From this type of analysis, the term in vitro-in vivo correlation (IVIVC) evolved. Numerous IVIVC studies are in the literature. Controlled release products, rather than immediate release products, are the focuses in the IVIVC literature. Similarly, compendial and regulatory guidance (1,2) has been provided for controlled release products. IVIVC analysis for controlled release products is well accepted. Notable is that IVIVC analysis for immediate release products have been less successful (1). This disappointment with immediate release products has perhaps resulted in a generally low expectation for IVIVC success for immediate release products, including the questioning of the appropriateness of subjecting immediate release products to IVIVC.

A reason for this lack of success and acceptance may be the general failure of the Level A method to immediate release products. As noted above, Level A has traditionally been the most common IVIVC approach and requires a linear(ized) relationship between fraction drug absorbed and fraction drug dissolved.

However, this reason to reject IVIVC analysis for immediate release products is poorly founded. Since only products with dissolution rate-limited absorption (and with complete absorption) can be expected to exhibit a Level A plot with a slope of one and zero intercept (3), immediate release products will "fail" the Level A method, as generally is the case (1). Only products with significantly dissolution rate-limited absorption (and essentially complete absorption) will exhibit an IVIVC plot that fits the Level A description [e.g. Fig. 1] (3).

The intrinsic inability of immediate release products to conform to a Level A "straight line" appearance does not indicate that dissolution from such products fails as a surrogate for bioavailability. Also, the "failure" of immediate release products to exhibit dissolution rate-limited absorption should not infer that immediate release products are inappropriate candidates for other more relevant forms of IVIVC analysis (i.e. non-linear forms of IVIVC). Of course, the relevance of a dissolution test needs to be defendable in terms of the mechanism of drug release from the dosage form, including the role of physicochemical and physiologic factors (4).

The Slippery Slope of "Correlation"

So what are more relevant forms of IVIVC, that may apply to immediate release (IR)? Since dissolution is perhaps not rate-limiting in an IR product, the Fa against Fd profile will be non-linear. Figure 2 plots the Fa versus Fd profile for an IR product. Points in the profile do not follow the line of unity (i.e. Level A profile), but rather well below it, since absorption cannot "keep up" with dissolution.

![Figure 2](http://dissolutiontech.com/DTResour/800Articles/800_art1.html)

Figure 2. Fa versus Fd profile for enalapril maleate tablets. Dissolution is more rapid than overall absorption, resulting in a non-linear profile.
Why might we feel uncomfortable with such a plot? Some dissatisfaction may arise from our expectation of an IVIVC. In IVIVC, “C” denotes “correlation”, which is defined as “the degree of relationship between two variables” (5). Correlation deals with the “tightness” in how two variables vary together. This term does not limit a relationship to only the linear type, but allows for non-linear relationships as well.

However, the most simple relationship (and thus the most appropriate to consider first) is the linear relationship. When one speaks of correlation, a linear relationship is immediately considered and inspected for. In practice, correlation is often taken to imply a linear relationship. For IR products, this limitation is problematic. Arguably, avoidance of the word “correlation” and the use of a more general term that would allow for non-linear relationships may aid in the development of IVIVC-type analysis of IR products.

IVIVR
One possible substitution for IVIVC is IVIVR, with “R” denoting “relationship.” By comparison with Level A IVIVC, IVIVR analysis would concern the elucidation of the in vitro dissolution - in vivo absorption relationship. Hence, IVIVR need not be limited to straight-line relationships, which appear to be generally incorrect for IR products (1, 6, 7). One intent of IVIVR should be to learn about the relative contribution of dissolution to a product’s overall absorption kinetics.

One model for IVIVR is (3):

\[
F_a = \frac{1}{f_a} \left( \frac{1-\alpha}{\alpha-1} \left( 1- F_d \right) + \frac{1}{\alpha-1} \left( 1- F_d \right)^\alpha \right) \quad \text{eq 1}
\]

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 \( t = \# \),
- \( \alpha \) is the ratio of the apparent first-order permeation rate constant (kpaap) to the first-order dissolution rate constant (kd), and
- \( F_d \) is the fraction of drug dose dissolved at time \( t \).

Of note is that the Level A method is a special (linear) case of eq 1. If \( f_a = 1.0 \) (i.e. complete absorption) and \( \alpha \gg 1 \# \) (i.e. strongly dissolution rate-limited absorption), then \( F_a = F_d \), as in Fig 1.

This IVIVR analysis has been applied to several formulations of metoprolol, piroxicam, and ranitidine (6, 7). IVIVR analysis indicated that formulation properties and drug substance biopharmaceutic properties influenced the degree to which dissolution controlled overall absorption kinetics. Interestingly, dissolution was not rate-limiting from even the slowest dissolving IR formulations for the high solubility drugs.

**Future Directions**
The use of the term IVIVR rather than IVIVC is preferred. Immediate release products are amenable to dissolution-absorption analysis. However, the term IVIVR itself is neither new (8), nor fundamental. Rather, what is needed is a better understanding of in vivo dissolution, and its in vitro surrogate, the dissolution test. Additionally, dissolution needs to be considered in the context of other parallel and sequential processes (e.g. permeability, degradation, and transit). Through a better understanding of dissolution, dissolution and IVIVR can facilitate not only SUPAC-type changes, but also facilitate drug product development.

**References**


