Developing an IVIVC: Time Spent = Time Wasted

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The development of IVIVC is often described as follows: In vitro in vivo correlation (IVIVC) is an important concept and a tool in the development and evaluation of pharmaceutical dosage forms, especially modified release dosage forms. The objective of developing an IVIVC is to establish a predictive mathematical model describing the relationship between an in vitro property and a relevant in vivo response.

The objective of IVIVC, therefore, is to establish a relationship between in vitro (dissolution) and in vivo response (in vivo dissolution). The in vivo dissolution is derived or calculated from a plasma drug concentration-time (C-t) profile. Conversely, IVIVC is also described as a relationship between C-t profile and in vitro response (dissolution). In this case, in vitro dissolution results are to be converted or predicted to C-t profiles. These in vitro and in vivo responses are then plotted against each other to obtain a straight line (which is considered as the mathematical model).

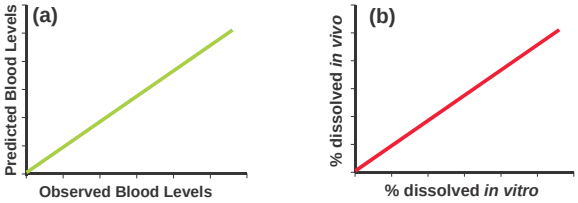

Figure 1: Schematic representations of mathematical model or correlation for IVIVC purposes

Aside from practical and procedural difficulties and complexities, which are enormous, for deriving and/or converting in vitro dissolution results to in vivo response (C-t profile) and vice versa, let us assume that one obtains ***perfect*** relationships, as straight lines with a correlation coefficient (R)=0.999 as shown in the Figure 1. The question is what would one do with these relationships or lines? How would these lines help in the development and evaluation of a product? How should these relationships or lines be used for predicting corresponding in vivo and/or in vitro product characteristics? For example, suppose an analyst has dissolution values or plasma drug levels at different sampling times for a product which is under development. How should the analyst plot the values on these (IVIVC) graphs, as these graphs only have percentages or concentrations on both axes, while the analyst has the values/results with sampling times? Obviously these relationships/lines cannot be used, it is a mathematical impossibility. It is no wonder then that there are no reports available in the literature which have used IVIVC (lines) to predict corresponding in vitro or in vivo results. This is simply not possible.

Therefore, it should be noted that developing an IVIVC, as presently described, cannot be used for the assessment and development of pharmaceutical products.

However, on the other hand, what is needed, for the development of products, is the prediction of C-t profiles from dissolution results of the test products. Such profiles can be obtained by merging in vitro dissolution results with the pharmacokinetic parameters of the ***drug***. This merging step is commonly, or formally, known as the convolution technique. Furthermore, this merging or convolution step ***does not*** require the development of an IVIVC either, it is an independent step. In this regard, a simple and practical approach, based on convolution principles, to obtain plasma drug concentration-time profiles has been described (link).

The need for the products development and evaluation is the predictability of C-t profiles, therefore, for clarity perhaps one should use the proposed terminology of IVIVP (in vitro to in vivo profiling) not IVIVC (see link).

In conclusion, developing an IVIVC as suggested presently is an unnecessary and not a useful exercise and should be considered as a waste of time. Furthermore, IVIVC cannot be used for the evaluation and development of pharmaceutical products. A simple suggested approach based on convolution principles may be more appropriate and useful.