Predicting plasma drug levels does not require an IVIVC development. In fact IVIVC cannot be used for such predictions at all, as explained with an example from literature for gliclazide ER products

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It is often suggested that conducting IVIVC studies, i.e. developing a relationship between in vitro (dissolution) and in vivo (plasma drug level), are necessary for developing dissolution tests capable of reflecting or predicting plasma drug levels. Unfortunately, this is not a correct view, as explained below:

In vitro/in vivo correlation (IVIVC): FDA guidance defines IVIVC as "A predictive mathematical model describing the relationship between an in vitro property of an extended release dosage form (usually the rate or extent of drug dissolution or release) and a relevant in vivo response, e.g., plasma drug concentration or amount of drug absorbed." According to this definition, the exercise requires development of a relationship, a mathematical model or equation, to describe the relationship. However, as explained previously, the development of a model or equation does not allow its use in predicting or estimating plasma drug levels from dissolution results.

Drug dissolution: On the other hand, FDA guidance for drug dissolution testing describes the need for drug dissolution as "drug absorption from a solid dosage form after oral administration depends on the release of the drug substance from the drug product, the dissolution or solubilisation of the drug under physiological conditions, and the permeability across the gastrointestinal tract." This clearly indicates that drug absorption depends on drug dissolution i.e. a relationship between dissolution and absorption exists. In fact, existence of this relationship/link between dissolution and absorption (and by extension plasma drug levels), forms the basis for conducting dissolution testing.

In reality, it is not the relationship or mathematical model between dissolution and absorption/plasma drug levels which needs to be developed ***but*** the need is that of a method to convert dissolution results into absorption/plasma drug levels ***using an existing relationship between the two***. Considerable confusion exists in the literature in this regard, which hinders in developing appropriate methods to convert dissolution results into plasma drug levels. It also prevents the proper use of drug dissolution testing for products development and evaluation.

This article is an attempt to explain the cause of this confusion and offer a solution to address this situation based on an example from literature (*the publication*) describing IVIVC development for extended release (ER) products as per current practices and requirements.

In *the publication*, results of a bioavailability study have been reported using two gliclazide ER 60-mg tablet products. Also reported are results from a dissolution study based on two sets of experimental conditions using two different media (0.1 M HCl and phosphate buffer pH 7.4) and two rpms (100 and 50). For the convenience of the readers, the dissolution profiles are reproduced in Figure 1. Observing the figure, the dissolution behaviour of products does not appear very different under different test conditions. Similar opinion has also been expressed in *the publication*. However, authors chose the results obtained using HCl as medium with rpm set at 50 for IVIVC development, as it showed the most discrimination between slow and fast release type formulation with f_2 (similarity factor)=40.

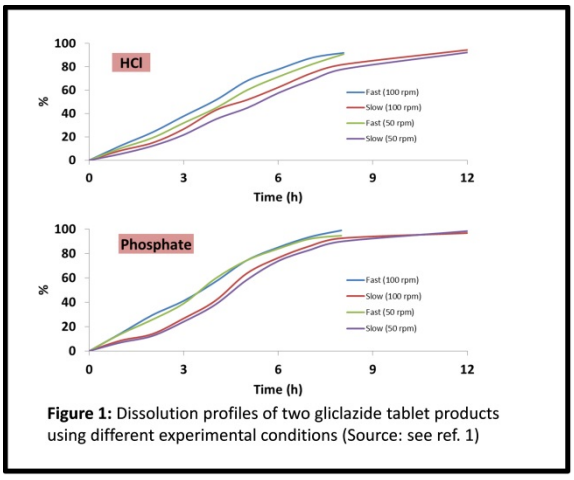

Figure 1: Dissolution profiles of two gliclazide tablet products using different experimental conditions (Source: see ref. 1)

In reality, authors are making a selection of results (perfectly as per current thinking and requirements) which would reflect the observed differences in dissolution results with those observed from the bio-studies. Therefore, in reality, one does not develop a relationship but ***seeks*** a ***match*** of in vitro dissolution results with those of bio-results. Unfortunately, people do not develop IVIVC but seek experimental conditions

for dissolution testing which will provide matching results to in vivo results.

From the physiological or absorption perspective, however, it is a very well-known fact that drug absorption does not occur, at least in most cases, from the acidic (stomach) environment but rather from higher pH environment (intestine). Therefore if one would like to link in vitro dissolution with absorption then one has to consider higher pH environment not the lower pH environments. Thus, based on physiological requirements comparing dissolution results at pH 1 would not be accurate. The point being that although suggested and required, the current practices of IVIVC development are not based on scientific reasoning or merit.

The IVIVC was considered developed, as described in the publication, based on the deconvolution method i.e. in vivo dissolution results were extracted from plasma drug levels and compared/plotted against the in vitro dissolution results. This provided an equation (model): $y = 1.2437x + 4.7565$ with R=0.9607 representing appropriate and successful IVIVC. Note "y" and "x" in the model represent percentages or fractions of drug release, in vivo and in vitro, at the same time points.

The question now is, how will one use the equation (obtained from IVIVC) to predict drug levels from dissolution results. One cannot, because, one only has dissolution results which are reported as percent/fraction with time, the model uses percentages/fractions without a time scale. Thus, the developed model (equation) cannot be used for dissolution results. Secondly, the model is based on only percentages/fractions of drug dissolved in vitro or in vivo, not the plasma levels, therefore, it has no ability to predict plasma drug levels. Obviously, this exercise of IVIVC development based on deconvolution method will be useless for predicting plasma drug levels; the main objective of the developing IVIVC.

As stated earlier that the main objective of conducting a dissolution test is to be able to estimate or predict plasma drug levels or simply conversion of dissolution results/profiles into plasma drug levels. It is similar to the practice of calculating drug concentration/percentages from UV absorption values by using slope and intercept values obtained from the calibration curve. Similarly dissolution results are to be converted into plasma levels by using drug PK parameters. This conversion step is called convolution. The detailed procedure of this conversion is provided here and here.

Considering this background, dissolution results described in *the publication* using phosphate buffer (100 rpm) are converted into plasma levels. The reason for selecting this set of experimental conditions (100 rpm/phosphate buffer) is that for predicting plasma levels, as stated above, one should always try to use results obtained employing the intestinal environment. The reason of selecting 100 rpm and not the 50 rpm is because it is known that 50 rpm often causes a cone formation or product stagnation within dissolution vessels, which results in artificially low dissolution results.

The predicted plasma profiles are shown in Figure 2 along with corresponding dissolution profiles which were used for the prediction.

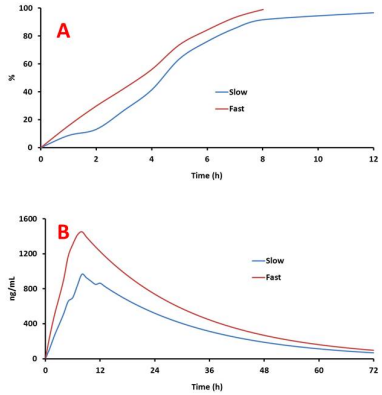

Figure 2: (A) Dissolution profiles of two products using phosphate buffer; (B) predicted plasma drug levels obtained from the dissolution profiles shown above.

The next question is how results from these two predicted profiles should be evaluated or compared quantitatively. As these profiles look similar to plasma drug levels obtained from bio studies, they should therefore be evaluated just like any bio-profile as well i.e. using C_{max} and AUC parameters. Table 1 provides values of the parameters from the bio-studies (as described in *the publication*) and from the predicted profiles.

Table 1: PK parameters value as reported from human bioavailability studies [1] *vs* predicted from dissolution results

		From bio-study	Predicted
Slow	C_{max} (ng/ml)	1064	966
	T_{max} (h)	8	8
	AUC	41454	27511
Fast	C_{max} (ng/ml)	1373	1452
	T_{max} (h)	8	8
	AUC	41275	40663

The predicted values compared well with those reported from the bio-studies (as per *the publication*). A discrepancy in the values of AUC (predicted vs actual) for the slow release product is noted which is difficult to explain.

In conclusion:

(1) IVIVC means developing of a relationship, model or equation, which does not provide a means to predict plasma drug levels.

(2) In reality, currently used practices of developing IVIVC do not even develop a relationship, but seek experimental conditions which may provide matching in vitro results for the in vivo results.

(3) The convolution method as described here, and previously, is to be used for the prediction of plasma drug levels.

(4) The convolution method as described here predicted the plasma drug levels from dissolution results fairly accurately.

(5) The predicted values of PK values are similar to those obtained from in vivo study with similar conclusions.

(6) The described convolution method is a simple, efficient and product/drug independent approach for predicting plasma drug and may be used during product development and later for the evalautions.

Reference:

Mandal, U., Ray, K.K., Gowda, V., Ghosh, A., Pal, T.K., 2007. In-vitro and in-vivo correlation for two gliclazide extended-release tablets. J. Pharm. Pharmacol. 59, 971–976.