dx.doi.org/10.14227/DT150108P6

IVIVC: Methods and Applications in Modified-Release Product Development

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The in vitro–in vivo correlation (IVIVC) for a pharmaceutical product is a mathematical relationship between an in vitro property of the product and its in vivo performance. The in vitro release data of the active substance normally serve as characteristic in vitro property, while the in vivo performance is represented by the time course of the plasma concentration of the active substance. These data are then treated mathematically to determine whether a correlation exists; a correlation can usually be expected when drug release from the product is the step governing the subsequent absorption kinetics. This is an essential design element for a modified-release dosage form. For oral dosage forms, the in vitro drug release is routinely measured and characterized as dissolution rate. The included figures provide a step-by-step procedure for the development of the IVIVC.

The relationship between the in vitro and in vivo characteristics is expressed mathematically by a linear or nonlinear correlation. However, the plasma concentration profiles cannot be related directly to the in vitro release rate; they have to be converted first to the underlying in vivo release or absorption data, either by pharmacokinetic compartment model analysis or by linear system analysis. The latter is usually accomplished mathematically by using the deconvolution/convolution method. This method requires the availability of a weighting function for the "body system," the unit input response. Normally this is the in vivo performance of an immediately available dosage form, like an oral solution or a rapidly dissolving tablet. The numerical deconvolution/convolution method is more general and thus preferred because it does not make any pharmacokinetic model assumptions. Using a pharmacokinetic compartmental analysis approach, the in vivo absorption rate can be calculated when the pharmacokinetic parameters of the drug substance are known. In both approaches, either the weighting function or the pharmacokinetic constants should ideally be available from the same study group used for characterizing the performance of the modified-release dosage form. The correlation is normally specific to one formulation type (i.e., the same rate-controlling release principle).

The IVIVC calculation is based on average in vitro and in vivo data. From a regulatory standpoint, the in vitro data are considered acceptable for an IVIVC when the dissolution rate is an average of 12 individual determinations and the coefficient of variation at each sampling point is below 10% (the first release data may have a larger variability). Likewise, the mean plasma concentration data from a homogeneous study group with *n* as low as 6 can provide reliable data for the development of an IVIVC. However, the size of the study group should depend on the variation in the biological data. Averaging the in vivo data will result in different C_{max} values than are normally reported in bioavailability studies. For this application, it will be the highest value in the averaged profile and not the mean of the highest concentrations observed in the individual profiles.

An IVIVC that correlates the entire in vitro and in vivo profiles has regulatory relevance and is called a Level A correlation. The quality of the correlation is tested with its prediction power. As described in regulatory guidelines, the deviation between prediction and observation is tested either with the data used for developing the correlation (so-called internal validation) or with data sets that were not used for the generation of the IVIVC (external validation). The allowable percent deviation is defined in the guidelines. In the regulatory context, the power of the prediction is assessed only with regard to C_{max} and AUC.

The IVIVC becomes more robust when three or more different formulations are tested in the same in vivo study

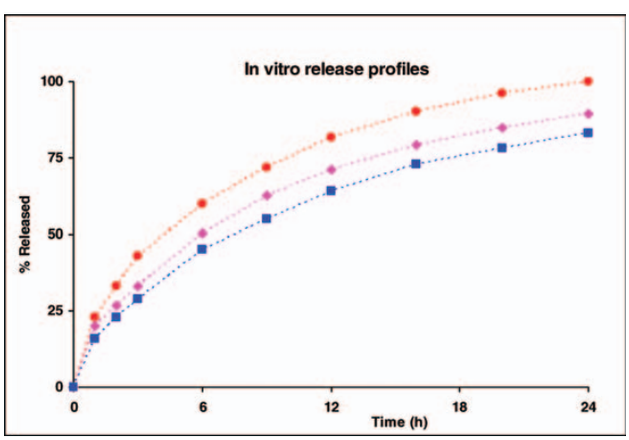

Figure 1. The in vitro release from three prototype ER formulations, where the middle one is normally the intended formulation for marketing. The in vitro release from the faster and slower prototypes differs ideally by around 10% on average. In this example, the f_2 values are 52.4 for the faster formulation and 61.4 for the slower one, when compared with the target formulation.

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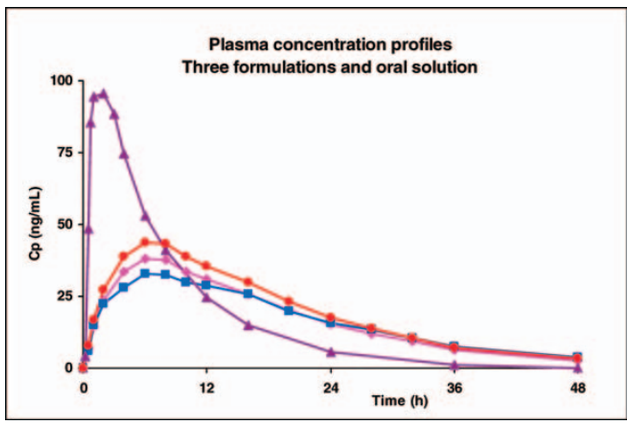

Figure 2. The mean in vivo performance of the three formulations, as well as the plasma concentration profile from a solution of the drug, observed in the same study group in a cross-over design. The number of subjects is chosen such that reliable average profiles are obtained. By visual inspection, a rank order relationship with the in vitro performance can immediately be detected.

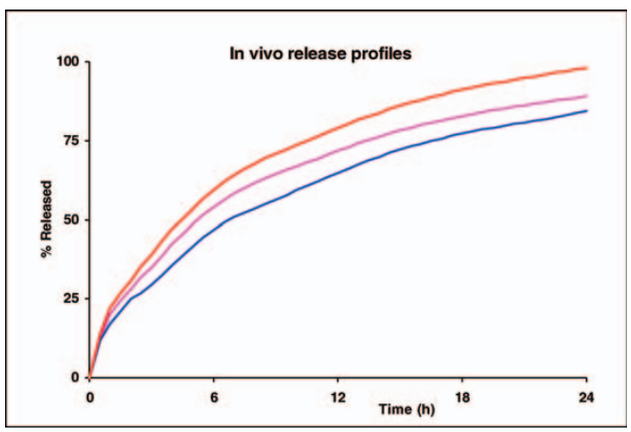

Figure 3. In a first step of the IVIVC development, the in vivo release profiles from the three formulations are derived from their plasma concentration profiles, here by applying the deconvolution method using the profile from the drug solution as unit impulse response or weighting function.

in addition to the product serving for the pharmacokinetic or weighting function information. A correlation based on two differing formulations can be considered on a limited basis. For the development of an IVIVC, the release controlling excipient(s) in the formulations should either be identical or very similar. Ideally, in vitro dissolution data sets should be obtained with different test conditions. The in vitro data set leading to an IVIVC with the smallest prediction error is then selected for further use because, based on the IVIVC, it is considered most bio-indicative.

The application of the IVIVC consists of selecting the bio-relevant in vitro test method as just described and

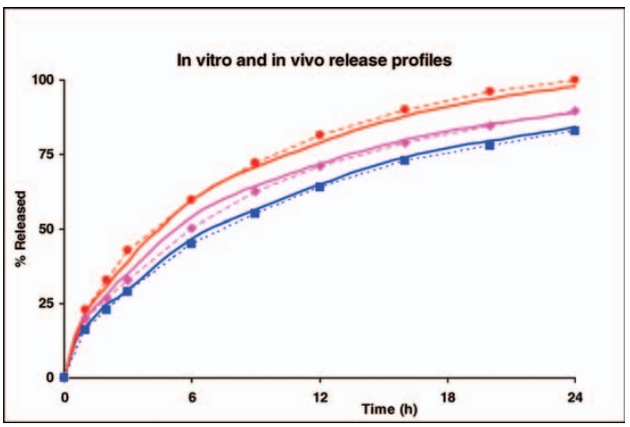

Figure 4. The in vivo release profiles are then superimposed on the in vitro release profiles. The good fit promises a reliable correlation and indicates that the release kinetics are similar in vitro and in vivo (i.e., no time scaling of the in vitro data is necessary).

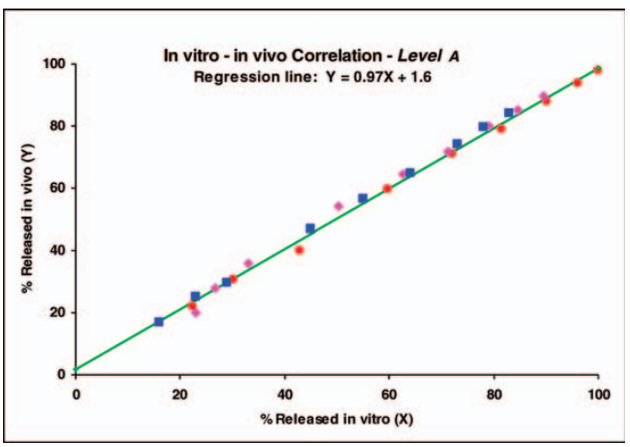

Figure 5. The percent released in vitro are then plotted against the percent released in vivo for the same time points. In this case, a linear correlation is the result. The equation of the regression line is the IVIVC model, which is then used for validating the model. A validated (i.e., acceptable) model can then be used to calculate the allowable in vitro release rate corridor of the formulation such that a lower and upper side batch would still be bioequivalent, based on acceptable point estimates of C_{max} and AUC.

calculating the maximum acceptable spread in the in vitro release range to assure bioequivalence from batch to batch. The release specifications for the upper and lower side batches are calculated with the IVIVC such that they are still bioequivalent based on point estimates of C_{max} and AUC.

Another important application of the validated IVIVC is to serve as justification for a biowaiver in filings of a Level 3 (or Type II in Europe) variation, either during scale-up or

post approval, as well as for line extensions (e.g., different dosage strengths). Of course, a biowaiver will only be granted if the prediction of the in vivo performance of the product with the modified in vitro release rate remains bioequivalent with the originally tested product (i.e., the new dissolution rate remains within the IVIVC based biorelevant corridor).

In conclusion, a Level A IVIVC is a valuable development tool that can lead to substantial time and cost savings during and after the development of a modified-release product. It ought to be considered as a milestone for each development plan of such a dosage form. However, developing an IVIVC and applying it must also make therapeutic sense. An IVIVC for a drug with a narrow therapeutic index, for a prodrug, or for a drug with varying first-pass effect is of limited use even if the mathematic correlation seems to suggest a reliable prediction of the in vivo performance.