can be accomplished by using data from the formulations used to build the model (internal validation) or by using data obtained from a different (new) formulation (external validation). While internal validation serves the purpose of providing a basis for the acceptability of the model, external validation is superior and affords greater "confidence" in the model.

Generally, a plot of the fraction of drug absorbed (F_a) against the fraction drug dissolved (F_d) is made, wherein the fraction absorbed is obtained by deconvoluting the plasma profile. Often the goal is to develop a profile that need not a priori be a linear or even a predefined function. For example,

$$F_a = \frac{1}{f_a}\left(1 - \frac{\alpha}{\alpha - 1}(1 - F_d) + \frac{1}{\alpha - 1}(1 - F_d)^{\alpha}\right) \tag{5.17}$$

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 $t = \#$, α is the ratio of the apparent first-order permeation rate constant (k_{paap}) to the first-order dissolution rate constant (k_d), and F_d is the fraction of the drug dose dissolved at time t.

5.3.5.1 Internal Validation

Using the IVIVC model, for each formulation, the relevant exposure parameters (C_{max} and AUC) are predicted and compared with the actual (observed) values. The prediction errors are calculated using:

$$\text{Prediction error (\% PE)} = [(C_{max,observed} - C_{max,predicted})/ C_{max,observed}] \times 100 \tag{5.18}$$

The C_{max} can be replaced with corresponding AUC. The criteria set in the FDA guidance on IVIVC are as follows: for C_{max} and AUC, the mean absolute percent prediction error (% PE) should not exceed 10%, and the PE for individual formulations should not exceed 15%.

For establishing external predictability, the exposure parameters for a new formulation are predicted using its in vitro dissolution profile and the IVIVC model, and the predicted parameters are compared with the observed parameters. The PEs are computed as for the internal validation. For C_{max} and AUC, the PE for the external validation formulation should not exceed 10%. A PE of 10–20% indicates inconclusive predictability and illustrates the need for further study, using additional data sets. For drugs with a narrow therapeutic index, external validation is required despite acceptable internal validation, whereas internal validation is usually sufficient with nonnarrow therapeutic index drugs.

Several commercial software programs are available to study IVIVC; for example, PDx-IVIVC (3), which is a comprehensive IVIVC software program that performs deconvolution, calculating the fraction or percentage of drug absorbed and correlating it with in vitro fraction or percent of dissolved data. It also allows Level C correlations (single or multiple), wherein a single-point relationship between a dissolution parameter, for example, percent dissolved in 4 hours and a pharmacokinetic parameter (e.g., AUC, C_{max}, and T_{max}), is determined. A successful IVIVC model can