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Combined Models for Data From *In Vitro-In Vivo Correlation* Experiments

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Summary

A method is presented to describe the *in vitro-in vivo correlation* (IVIVC) of an extended release drug formulation. This extended release drug product is overencapsulated with immediate release material. The heterogeneity of the capsule is modelled using a combined model of an extended release and an immediate release pharmacokinetic profile. Whereas an IVIVC is conventionally performed using a two-stage procedure, the model uses a one-stage convolution-based method. The method is applied to a Galantamine controlled release formulation, an acetylcholinesterase inhibitor for the treatment of Alzheimer's disease. The average percentage prediction error indicated a good fit of the new model.

Keywords: controlled release; convolution; dissolution curve; IVIVC; one-stage model fitting.
Running title: Mixture Distributions to Model IVIVC Experiments

1 Introduction

In Vitro-In Vivo Correlation (IVIVC) is commonly used in preclinical and clinical biopharmaceutical research. It establishes a valuable link between the *in-vitro* dissolution and the

in-vivo release of the investigational drug. Based on this link, the controlled release pharmacokinetic profile can be predicted from a subject's immediate release plasma concentrations profile and the *in-vitro* dissolution profile using the IVIVC model. If a controlled release capsule dissolves differently, this change in *in-vitro* dissolution properties can be translated into the corresponding altered *in-vivo* pharmacokinetic profile once an IVIVC is established.

IVIVC models are commonly used in a wide range of applications. One can use the IVIVC to claim that the differences observed *in-vitro* between two batches do not affect the drug exposure by predicting the *in-vivo* plasma concentration-time profile. Similarly, one can state that manufacturing changes of the controlled release formulations do not affect the drug exposure. Thus no expensive *in-vivo* bioequivalence testing is required for either situation (Hayes et al. 2004). This technique can also be applied in formulation development. The formulation can be modified such that the plasma concentrations remain within the therapeutic window over a sufficient period of time.

The first methodological work on IVIVC was done two decades ago (Gillespie and Veng-Pedersen 1985) with the introduction of the deconvolution method: deconvolution extracts the *in-vivo* release based on the fact that controlled release plasma concentrations equal the convolution of immediate release plasma concentrations and the *in-vivo* release. The latter is then linked to the *in-vitro* dissolution results. Dunne *et al.* (2005), however, proved that the deconvolution method might give biased results. Gillespie (1997) and O'Hara *et al.* (2001) improved the method by directly modelling the convolution itself, without explicitly calculating the *in-vivo* release, using a two-stage approach.

Our methodology presented in this paper also uses the convolution approach and extends previous work in two respects. The two-stage approach is replaced by a one-stage approach and contrary to other published results (Modi *et al.* 2000, Veng-Pedersen *et al.* 2000) a heterogeneous formulation is used in the IVIVC model. The formulation contains an extended release part overencapsulated with immediate release material, and will be referred to as controlled release capsule in the remainder of the paper.

The rest of the paper is organized as follows. The case study, motivating this research,

is described in Section 2. The dissolution models applied in this paper are described in Section 3.1. The convolution-based models described by O'Hara *et al.* (2001) used for IVIVC can be found in Section 3.2.1. Extension of these models including a combination model is described in Section 3.2.2. The results of applying the proposed methodology to the case study are reported in Section 4.

2 The Case Study

The acetylcholinesterase inhibitor Galantamine is used for the treatment of Alzheimer's disease (Lilienfeld 2002). Galantamine formulations currently on the market are tablets, a syrup and extended-release capsules.

Within the population of subjects with Alzheimer's disease, the duration of drug exposure can sometimes be too short to guarantee sufficient protection for a certain time period due to poor compliance. Therefore, a controlled release formulation of Galantamine was developed in an attempt to optimize drug exposure. Whereas an immediate release formulation dissolves instantaneously and the drug product is immediately available, an extended release formulation releases the drug product slowly over time allowing the body to absorb the drug product gradually. The controlled release formulation under investigation here consisted of the extended and immediate release components combined in the same pellet as 2 layers (ratio CR/IR: 3/1) separated by a rate-controlling membrane containing 5-12% ethylcellulose/hydroxypropyl-methylcellulose (EC/HPMC; ratio: 75/25). The relatively high water solubility (3.3 g/100 $m\ell$ water, pH=5.2) and absolute oral bioavailability (88.5%) of Galantamine are pharmaceutical characteristics indicative of a drug whose controlled release formulation is a good candidate for IVIVC exploration.

Four different controlled release formulations were studied (slow, fast, between and medium), however for the sake of simplicity the focus is only on one controlled release formulation (the slow one). For each controlled release formulation, twelve dissolution curves were assessed *in-vitro*. The dissolution data were generated using an USP apparatus 2 - paddle with 50 rpm (s.e. 2 rpm) speed of shaft rotation. The dissolution medium used was

a volume of 900 $m\ell$ of 0.050 M phosphate buffer at pH 6.5. The percentage dissolution was registered between 0.5 and 18 hours, as shown in Figure 1 for a controlled release formulation.

Seventeen subjects were first assigned to the immediate release formulation and then randomized according to a four period latin square design. Treatments were four controlled release formulations (slow, fast, between and medium) of Galantamine. One subject dropped out after the immediate release period. He did not receive the controlled release formulations and was included as such in the analysis. To demonstrate our methodology, only one of the four controlled release formulation, the slow one, is included in this analysis. A venous blood sample was taken for the measurement of Galantamine plasma concentrations at specified time points during the study, from pre-dose (0 hour) until 60 hours post-dose for the immediate release formulation, and up to 72 hours post-dose for the controlled release formulations.

The immediate release plasma concentration-time data are shown in Figure 2, while the plasma concentration-time data for the controlled release formulation are presented in Figure 3. In the former, maximal plasma concentrations were reached faster and were higher, but they decreased rapidly. In the latter, a bimodal profile was present: one steep peak was present after 30 minutes followed by a second smoother peak 6 hours after intake. In addition, the decrease of plasma concentration is slower after the second peak.

The advantage of combining the extended and immediate release formulation lies in this bimodal profile. The goal of the extended release part is to ensure that patients remain in the effective plasma concentration range from 3-4 until 24 hours, and therefore it is hoped that the patients remain protected for the full 24 hours. The extended release fraction on it own would not reach the therapeutic window quickly enough; levels would remain too low during the first 3 hours post-dose. Therefore, a loading dose consisting of an immediate release fraction, is added. Hence, patients remain protected for the full 24 hours.

3 Methodology

First, four types of models used for describing the *in-vitro* dissolution curves are introduced in Section 3.1. Then the *in-vivo* convolution-based IVIVC methodology described by O'Hara *et al.* (2001) is described in Section 3.2.1, followed by the newly proposed convolution model in Section 3.2.2, the model fitting in Section 3.3 and the goodness-of-fit in Section 3.4.

The following notation will be used. The index 1 denotes the *in-vitro* data, while 2 will be used for *in-vivo*, i is the statistical unit representing the capsule for *in-vitro* and subject for the *in-vivo* data; k denotes the formulation; The immediate release formulation however will be denoted with δ instead of k due to its special status in IVIVC modelling and to emphasize that the underlying probability density function of the release mechanism follows in this case the Dirac Delta distribution. F will denote the actual dissolution/release fraction; c stands for the actual plasma concentration profile, and more specific, $c_{i2\delta}$ is the actual immediate release plasma concentration profile, also referred to as the unit impulse response. This is traditionally but not necessarily, based on a compartmental model. Y_1 stands for the measured dissolution for the *in-vitro* data, Y_2 for measured plasma concentration *in-vivo*. For example, Y_{i2k} denotes the measured controlled release plasma concentration of subject i for formulation k.

3.1 *In-Vitro* Dissolution Models

The *in-vitro* dissolution profile is often described by a Weibull function (Comets and Mentré, 2001). Besides the Weibull function, also a simpler exponential function and a more complex Gompertz *in-vitro* dissolution model will be evaluated.

The simplest model for the *in-vitro* dissolution profile is given by the exponential model:

$$\begin{aligned} Y_{i1k}(t) &= F_{i1k}(t) + \varepsilon_1, \quad \varepsilon_1 \sim N(0, \sigma_1^2), \\ F_{i1k}(t) &= \phi_1\{1 - \exp[-(t - \phi_3)\phi_{2i}]\}, \end{aligned} \tag{3.1}$$

with $0 < \phi_1 \leq 1$, $\phi_{2i} \sim logN(\phi_2, \sigma_{\phi_2}^2)$, and ϕ_{2i} the capsule-specific scale parameter and ϕ_3

a lag time. This model has a steep increase in the beginning and converges slowly to the asymptotic maximal dissolution, ϕ_1.

The following extension of the exponential model copes with the heterogeneity of the formulation via the ϕ_4-parameter.

$$\begin{aligned} Y_{i1k}(t) &= F_{i1k}(t) + \varepsilon_1, \quad \varepsilon_1 \sim N(0, \sigma_1^2), \\ F_{i1k}(t) &= \phi_4 + (\phi_1 - \phi_4)\{1 - \exp[-(t - \phi_3)\phi_{2i}]\}, \end{aligned} \tag{3.2}$$

where ϕ_4 captures an initial jump followed by the previous version of the exponential model.

The previous models, however, lack the capability to fit a sigmoidal curvature. Therefore, the traditional Weibull function with the initial jump ϕ_4 is proposed to check for the improvement under these conditions, see model 3.3. The parameter ϕ_2 has the same interpretation as for the exponential model, whereas ϕ_3 determines the shape.

$$\begin{aligned} Y_{i1k}(t) &= F_{i1k}(t) + \varepsilon_1, \quad \varepsilon_1 \sim N(0, \sigma_1^2), \\ F_{i1k}(t) &= \phi_4 + (\phi_1 - \phi_4)\{1 - \exp[-(t\phi_2)^{\phi_{3i}}]\}. \end{aligned} \tag{3.3}$$

The dissolution profiles in Figure 1 contain both an asymmetrical S-shaped curvature and an initial jump. The Gompertz curve has the first property, but it has its short curvature at the end. The following modification of the Gompertz function (Lindsey 1997) will serve to model this feature and to challenge the performance of the Weibull model:

$$\begin{aligned} Y_{i1k}(t) &= F_{i1k}(t) + \varepsilon_1, \quad \varepsilon_1 \sim N(0, \sigma_1^2) \\ F_{i1k}(t) &= \phi_4 + [\phi_{1i} - \phi_4] \exp\{-\exp[-\phi_2(t - \phi_{3i})]\}, \end{aligned} \tag{3.4}$$

where ϕ_4 represents the initial jump. The coefficient $\phi_{1i} \sim N(\phi_1, \sigma_{\phi_1}^2)$ corresponds to the asymptotic maximum dissolution. ϕ_{3i} represents a capsule specific lag-time, ϕ_2 is the scale parameter and is related to the inverse half-life of the curve.

3.2 *In-Vivo* Models

3.2.1 Convolution-based Models (O'Hara et al. 2001)

Gillespie and Veng-Pedersen (1985), Gillespie (1997), Dunne *et al.* (1999), O'Hara *et al.* (2001), and Hayes *et al.* (2004) showed, based on *in-vitro* dissolution data and *in-vivo* immediate release plasma concentrations, that the slow release formulation concentrations can be predicted and an IVIVC established using a convolution-based method. This method is more robust than the deconvolution method (Dunne *et al.* 2005), and it jointly fits a set of models.

The controlled release plasma concentrations at time t, denoted by $Y_{i2k}(t)$, for the ith subject taking treatment k, can be derived as the convolution of the unit impulse response $c_{i2\delta}$ and the *in-vivo* release curve F_{i2k} (Gillespie and Veng-Pedersen 1985):

$$\begin{aligned} Y_{i2k}(t) &= \int_0^t c_{i2\delta}(t-\tau)F'_{i2k}(\tau)d\tau + \varepsilon_2, \\ \varepsilon_2 &\sim LN(0,\sigma_2^2). \end{aligned}$$

The *in-vivo* release curve F_{i2k} can be considered as the cumulative distribution function of the stochastic process representing the release of the molecule into solution. Hence, F'_{i2k} represents the corresponding density function of the release of the molecule into solution. The unobserved *in-vivo* release cumulative distribution function can be linked to the *in-vitro* one using the following IVIVC model:

$$\begin{aligned} F_{i2k}(t) &= g^{-1}(\theta_0 + \theta_1 t + s_{ik} + g(F_{1k}(t))), \\ s_{ik} &\sim N(0,\sigma_s^2). \end{aligned}$$

The parameters θ_0 and θ_1 cope with dissolution changes in the gastrointestinal tract, whereas the random effect s_{ik} represents inter-subject differences of the intestines. The link function $g(\cdot)$ was set equal to the logit functions.

The method of O'Hara (O'Hara *et al.* 2001, Hayes *et al.* 2004) first estimates the subject-specific parameters of the immediate release profile using a compartmental analysis

and in a second stage simultaneously models the *in-vitro* dissolution curves as well as the convolution using the empirical Bayes estimates from the first stage.

3.2.2 Combination Models

All published models are limited to homogeneous formulations. A naive approach would be to ignore the heterogeneity of the formulation and fit the traditional model mentioned above for a homogenous formulation. However, in case of a heterogenous formulation of both immediate and extended release material, the cumulative distribution function does not start at 0 but rather at a quantity approximately similar to the proportion of immediate release material within the mixture. The inclusion of this initial jump alters the density function $F'_{i2k}(\tau)$. Therefore, we propose in this section a new model that takes this heterogeneity into account.

For the convolution model a similar derivation is possible. Recall from Section 2 that the capsules represent a heterogeneous formulation, consisting in part of immediate release and in part of extended release. As a result, two different underlying dissolution processes can be expected to be present.

The principle of superposition within pharmacokinetics, i.e., the assumption that each mechanism acts independently of each other and there is linear kinetics, means that the pharmacokinetic (PK) concentration-time profile of the controlled release formulation can be described as a weighted combination of each of the drug product PK-concentration-time profiles. This is a valid assumption (Piotrovsky *et al.* 2003). Based on this principle, one part of the profile corresponds to the immediate release drug product within the formulation, the other one corresponds to the extended release drug product. Clearly, these considerations imply a specific form for the model to be considered. The PK-profile corresponding to the immediate release drug product can be considered as identical to the one observed whereas the latter follows the convolution model as described in Section 3.2.1. Therefore, the following

new model is proposed:

$$\begin{aligned} Y_{i2k}(t) &= \phi_4 D c_{i2\delta}(t) + [\phi_1 - \phi_4]\, D \int_0^t c_{i2\delta}(t-\tau) F'_{i2k}(\tau) d\tau + \varepsilon_2, \\ \varepsilon_2 &\sim LN(0, \sigma_2^2), \end{aligned} \tag{3.5}$$

where ϕ_4 is the weight corresponding to the quantity of immediate release drug product within the formulation and D represents the dose. This corresponds to the initial jump observed in the *in-vitro* models.

Furthermore, the *in-vivo* release $F_{i2k}(t)$ model is slightly modified compared to the proposal of O'Hara *et al.* (2001):

$$F_{i2k}(t) = g^{-1}(\theta_0 + \theta_1 t + g(F_{i1k}(t))), \tag{3.6}$$

where the index i stands for the capsule i dependent variability of the *in-vitro* dissolution F_{i1k}. As this is unobserved for the capsule administered to the subject i, this is indirectly included via the subject level. Thus, the random effects are included at the *in-vitro* level of the model rather than as a random intercept. This corresponds to the underlying source of variation. Further, the gastro-intestinal subject level s_{ik} was removed from the IVIVC, because the inclusion of an additional random intercept, next to the presence of the random effect in the *in-vitro* part of the equation, could jeopardize convergence or lead to very long run-times. Additionally, one can only estimate these inter-subject gastro-intestinal differences when multiple formulations per subject are analyzed to enable the dissociation between subject- and vessel-driven variability.

Although it is not in the traditional sense, but this newly proposed combination model can be considered as a mixture distribution at two levels. A first mixture is situated in the *in-vitro* dissolution: it represents a mixture cumulative distribution function of a step function for the immediate release material of the formulation on one hand and a second cumulative distribution function such as the weibull distribution for the slow release product on the other hand. The mixture is also present at a second level: it is a combination of two log-normally distributed processes for the immediate release plasma concentration time-profile on one hand and the convolution based profile for the slow release product on the other

hand. Again, the weight ϕ_4 comes in to attribute the ratio of the two distinct underlying release processes.

3.3 Model Fitting

The models for the immediate release plasma levels and the *in-vitro* dissolution were initially fitted separately to obtain good starting values for fitting the IVIVC model. The immediate release pharmacokinetics of Galantamine are known to follow a two-compartmental model (Piotrovsky *et al.* 2003). This was based on population modelling of several studies in elderly patients:

$$\begin{aligned}
Y_{i2\delta}(t) &= c_{i2\delta}(t) + \varepsilon_{i\delta k}, \\
c_{i2\delta}(t) &= \frac{k_a}{V_F}\left(\frac{(k_{21}-\alpha_i)e^{-\alpha_i(t-t_{lag})}}{(k_a-\alpha_i)(\beta_i-\alpha_i)} + \frac{(k_{21}-\beta_i)e^{-\beta_i(t-t_{lag})}}{(k_a-\beta_i)(\alpha_i-\beta_i)}\right. \\
&\quad \left. + \frac{(k_{21}-k_a)e^{-k_a(t-t_{lag})}}{(\alpha_i-k_a)(\beta_i-k_a)}\right), \\
\varepsilon_{i\delta k} &\sim LN(0,\sigma_\delta^2), \qquad (3.7) \\
\begin{bmatrix} \alpha_i \\ \beta_i \end{bmatrix} &\sim N\left(\begin{bmatrix} \alpha \\ \beta \end{bmatrix}, \begin{bmatrix} \sigma_\alpha^2 & c_{\alpha\beta}\sigma_\alpha\sigma_\beta \\ c_{\alpha\beta}\sigma_\alpha\sigma_\beta & \sigma_\beta^2 \end{bmatrix}\right).
\end{aligned}$$

In this model, V_F is the apparent volume of distribution, t_{lag} is a lag-time, k_a is the absorption coefficient, k_{21}, α, and β are transfer rate constants. The best fit to the data was attained by choosing random effects on α and β, with associated variabilities σ_α^2 and σ_β^2. This was based on visual inspection of the fit of the individual profiles as well as by comparison of the likelihood functions. The absorption rate constant k_a could not be estimated by fitting the immediate release formulation alone because too few samples were taken during the absorption phase shortly after drug intake and k_a had to be fixed in the immediate release model.

A fundamental change to the convolution method of O'Hara (O'Hara *et al.* 2001) is that all models are fitted simultaneously, whereas O'Hara's method first fits the immediate release profile per subject and then in a second stage fits the convolution and the IVIVC using the empirical Bayes estimates of the immediate release PK-profile. A possible drawback of

such a two-stage modelling approach is that this might lead to biased results (Verbeke and Molenberghs 2000). By using a one-stage model, this source of possible bias is eliminated. The possible impact is discussed further in Section 5.

Traditionally in pharmacokinetic modelling, the model fit is verified at the individual subject level, i.e., the question is asked whether the model can fit each subject's plasma concentration profile. Thus a hierarchical model is used. In IVIVC modelling, one is not interested in the behavior of the individual capsules or subjects, but rather in the formulation itself, at the population level. In particular, the link between the *in-vitro* dissolution and *in-vivo* release process of the formulation is very important. Unlike in the linear setting, the marginal and hierarchical models do not coincide when the random effects are significant. Therefore, the random effects have to be integrated out to obtain the marginalized model. The marginalization of the hierarchical model was performed as follows: 10000 capsules were simulated and then averaged over. As such, the random effects were integrated out (Molenberghs and Verbeke 2005) and the model plotted.

The set of models was implemented in the SAS procedure NLMIXED (version 9.1). Model convergence was obtained using the first-order integration method of Beal and Sheiner (1982). The convolution integral itself was approximated with the trapezoid rule. An example of the SAS code can be found in the web appendix.

3.4 Goodness-of-Fit

Following the regulatory guidances (FIP 1996, CDER 1997) the adequacy of the proposed models was assessed using the average absolute percent prediction error ($\%PE$). This was defined as the mean of

$$\left| \frac{x_{obs,i} - x_{pred,i}}{x_{obs,i}} \right| \times 100, \tag{3.8}$$

where $x_{.,i}$ is the Area Under the Curve to the last measurable observation (AUC_{last}) or the maximal concentration (C_{max}) of the empirical Bayes estimates and the observed concentrations for subject i. Thus, for each observed and predicted profile per subject, the AUC_{last} and C_{max} were calculated and the above ratios were obtained. Given its skewed distribu-

tion, all ratios were log-transformed to better approximate normality, the mean and its 90% confidence interval was calculated and backtransformed.

$\%PE$ is known to be an optimistic goodness-of-fit metric. However, goodness-of-fit metrics are not the main topic of this paper. Therefore, the $\%PE$ criterion is applied so as to not detract attention from the modeling of an IVIVC in the case of a heterogenous formulation.

4 Results

As mentioned in Section 3.1, the modified Gompertz function fitted the data well. Random effects were added to ϕ_1 and ϕ_3 since, as seen in Figure 1, the asymptotic maximum dissolution was capsule dependent. The random effect on the lag time improved the fit further. Conventional model selection tools, such as the likelihood ratio or the Akaike Information Criterion, were used.

A system of sub-models is proposed for the IVIVC modelling consisting of the combining models 3.4, 3.5, 3.6, and 3.7. All four models are fitted simultaneously. This allows exchange of information between models. Whereas the absorption rate constant k_a could not be estimated for the immediate release model alone, owing to insufficient early sampling points, the pooling of information about common parameters from different data sources did allow for estimation of k_a for model 4. In models 1–3, $\log(k_a) = -3$ had to be fixed to allow convergence. Additionally, $\log(V_F) = -4.64$ had to be fixed in models 1–2. Some simplifications were done for the system of sub-models compared to the separate models: (i) No random effect was used on the α-component of the two-compartmental model because inclusion of this random effect made the model diverge (non-positive hessian matrix). While this seems a disadvantage, one ought not to forget that the models are highly non-linear and rather complex. Therefore, one should keep the complexity of the random effects structure within reasonable limits; (ii) The dissolution random effects ϕ_{i1} and ϕ_{3i} were forced to be independent otherwise estimation of the correlation could not be established: many observations are needed to accurately estimate correlations between random effects.

The following models were fitted: Model (1)–(2) using the exponential dissolution and logit link as a convolution and a combination model, Model (3) as a combination model with a Weibull dissolution and logit link function, and Model (4) as a combination model with a Gompertz dissolution and logit link. Model (2)–(4) are the newly proposed models to cope with the heterogeneity of the data. Estimates of the model parameters can be found in Table 1 for the four different dissolution curves.

The fit based on the different dissolution models was formally compared by Akaike's Information Criterion (AIC): 937.8, 880.3, 668.3, and 502.4 for model 1–4, respectively. The model prediction of the controlled release plasma concentration of a randomly chosen subject for the different models is depicted in Figure 4. The fit of the Gompertz odds model was judged based on visual inspection of the empirical Bayes estimates versus the observed controlled release profiles on the one hand (Figure 5) and the average absolute percent prediction error on the other hand. Figure 5 contains the observed as well as the model predictions for both the controlled and immediate release plasma concentrations as well as of the *in-vitro* dissolution of a randomly chosen subject and capsule.

The $\%PE$ of the different models can be found in Table 2. The first two columns correspond to the C_{max} and AUC_{last} as requested in the regulatory guidelines (FIP 1996, CDER 1997), the last represents AUC_{0-4} and is an indication of the model fit for the data up to 4 hours. The model with the exponential dissolution does not fit the data well. The addition of the combination model to the exponential dissolution does not improve the model. The *in-vitro* exponential mixture dissolution model however misses the S-shape as observed in the data, see Figure 1. Therefore, the model is extended to the Weibull model and the Gompertz model as a combination model. The $\%PE$ indicate a significant improvement of the model fit for models 3 and 4.

The parameter estimates for the immediate release part of the model show a permutation: values for α in models 1 and 2 have the same magnitude, and hence physiological meaning as β for models 3 and 4. The residual variance is lower for the latter models (standard deviation of 19 instead of 29). Some of the inadequacy of the first model is

demonstrated in the asymptotic maximal dissolution parameter ϕ_1. In theory, all material should dissolve. Even though dissolution is not fully complete after 18 hours, the *in-vitro* release profile contradicts this. The half-life of the dissolution ϕ_2 is estimated to be 0.1 for models 1 and 3 whereas models 2 and 4 produce an estimate of 0.3. This 3-fold difference might indicate that also model 3 is not free of issues. The estimated proportion immediate release formulation ϕ_4 is close to the known formulation heterogeneity ratio of 0.25 for all 3 models. The parameters θ_0 and θ_1 have no physiological meaning and differences between the models are difficult to interpret.

5 Discussion

A model with clear improvements over the standard IVIVC models at two levels is presented: It allows the fitting of formulations containing both extended and immediate release material and it is a true one-stage analysis method. We employed the SAS procedure Nlmixed rather than the standardly used NONMEM package.

All publications up to now have been limited to homogeneous formulations. In this paper, the convolution based method is extended for a heterogeneous formulation of both an immediate and an extended release drug product by a combination model. Four different models were evaluated during the model building: The first model used the convolution with the Exponential dissolution model and the logit link function. The average percent error $\%PE$ of both C_{max} and AUC_{last} remained well above the 10% criterion from the guidelines (FIP 1996, CDER 1997), see Table 2, indicating an inadequate model fit.

The model was therefore extended to the combination model with the logit link function because this used the underlying heterogeneous structure of the capsules and fitted a bimodal profile. The use of this combination imposes, however, no restriction on the model. It relies on the principle of superposition within pharmacokinetics, i.e., the assumption that each mechanism acts independently of each other and there is linear kinetics. The metabolism of the drug remains unchanged during the drug product release and only depends on the

amount of drug product released. The standard convolution model itself assumes already the superposition principle and linear kinetics. The $\%PE$ for C_{max} of this model remained in the same order of magnitude. The fit of the *in-vitro* dissolution data indicated however that further refining was required: the exponential model has a steep incline for the first hours and converges to its asymptotic limit, whereas the *in-vitro* dissolution data showed an asymmetric S-shaped curve. The model was finetuned with the use of the Weibull and the Gompertz model for the *in-vitro* dissolution in combination with the logit link function. This lead to a substantial decrease in $\%PE$. Although the $\%PE$ was well below 10% for all parameters, only the Gompertz model had the upper limit of the 90% confidence interval below 10% for AUC_{last}. The Gompertz model can be considered as the superior model given this better prediction of the overall exposure AUC_{last} and the ability to estimate all parameters of the model without fixing any of them.

This illustrates that traditional models should not be used in case of formulations consisting of both immediate release and slow release drug product. The risk of overfitting is limited given that the construction of the model is based on the formulation properties and the clearly bimodal profiles.

Models 3 and 4 meet the regulatory specifications on the point estimate, see Table 2. Whereas the guidelines (FIP 1996, CDER 1997) focus only on the mean $\%PE$ being less than 10% to conclude IVIVC predictability, this does not take into account the possible variability of the prediction. Even though the average might be less than 10%, a large variability of the individual $\%PE$ might indicate that some subject's controlled release profile is poorly estimated. Therefore, one should rather use the non-inferiority philosophy and look at the upper limit of the 90% confidence interval.

A second, more fundamental change to the convolution method of O'Hara (O'Hara *et al.* 2001) is that all models are fitted simultaneously, whereas O'Hara's method first fits the immediate release profile per subject and then fits in a second stage the convolution and the IVIVC using the empirical Bayes estimates of the immediate release PK-profile. A possible drawback of such a two-stage modelling approach is that this might lead to biased

results (Verbeke and Molenberghs, 2000). In the first stage, the immediate release PK-profile is reduced to a couple of summary statistics and residual error is ignored. In the second stage, these estimates are used as if they are error-free. Hence, the possible error of these coefficients will be reallocated to the remaining coefficients and as such introduce possibly bias. Fitting everything at once however does not ignore the error in the individual compartmental PK-parameters. On the contrary, it allows a pooling of information about common parameters of the immediate and the extended release model. This might lead to more accurate parameter estimation like for example the k_a in the case study. However, no formal comparison of the two approaches was performed yet. The advantage of the two-stage approach is that the parameter space is split. As a result, the two-stage approach is more flexible, in the sense of adding random effect, and model convergence is easier and faster.

It is not clear, based on these data, whether a modified sampling would have allowed for better estimation. Intuitively, additional early sampling might enhance estimation of the parameter k_a, but this was not formally established. On the other hand, only a limited number of blood samples can be taken for ethical and practical reasons. Therefore, the current sampling scheme is arguably the best feasible one: additional early samples might jeopardize later sampling.

In conclusion, a novel one-stage methodology was proposed as well as a combination model to cope with heterogeneous formulations in IVIVC testing. Based on the case study it was shown superior to the traditional model.

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Table 1: Parameter estimates (95% confidence interval) for Models 1–4 using a one-stage convolution-based approach.

	Model 1	Model 2	Model 3	Model 4
	Est.	Est.	Est.	Est.
Parameter	(95% CI)	(95% CI)	(95% CI)	(95% CI)
Immediate Release				
k_a (hr^{-1})				0.026
				(0.004 ; 0.163)
V_F (L)			0.00356	0.0018
			(0.00305 ; 0.00417)	(0.0003 ; 0.0121)
k_{21} (hr^{-1})	0.43	0.48	0.067	0.033
	(0.26 ; 0.73)	(0.28 ; 0.83)	(0.063 ; 0.071)	(0.005 ; 0.205)
α (hr^{-1})	0.37	0.41	2.54	2.57
	(0.23 ; 0.62)	(0.25 ; 0.69)	(2.13 ; 3.03)	(2.12 ; 3.11)
β (hr^{-1})	11.5	11.5	0.14	0.14
	(10.9 ; 12.1)	(10.9 ; 12.1)	(0.123 ; 0.16)	(0.12 ; 0.16)
σ_β	0.06	0.05	0.24	0.21
	(0.04 ; 0.09)	(0.03 ; 0.08)	(0.14 ; 0.33)	(0.13 ; 0.29)
σ_δ	0.29	0.29	0.19	0.19
	(0.26 ; 0.32)	(0.27 ; 0.32)	(0.18 ; 0.21)	(0.17 ; 0.21)
In Vitro Dissolution				
ϕ_1	1.02	0.91	0.91	0.88
	(0.98 ; 1.05)	(0.88 ; 0.94)	(0.89 ; 0.93)	(0.86 ; 0.90)
ϕ_2	0.12	0.31	0.14	0.29

Table 1: Parameter estimates (95% confidence interval) for Models 1–4. (continued)

	Model 1	Model 2	Model 3	Model 4
	Est.	Est.	Est.	Est.
Parameter	(95% CI)	(95% CI)	(95% CI)	(95% CI)
	(0.10 ; 0.13)	(0.28 ; 0.34)	(0.13 ; 0.15)	(0.28 ; 0.31)
ϕ_3	-1.74	0.72	1.39	4.07
	(-1.98 ; -1.50)	(0.46 ; 0.97)	(1.28 ; 1.50)	(3.83 ; 4.30)
ϕ_4		0.27	0.23	0.22
		(0.26 ; 0.28)	(0.21 ; 0.25)	(0.20 ; 0.24)
σ_1	2.95	2.33	3.26	1.33
	(2.54 ; 3.37)	(1.99 ; 2.66)	(2.82 ; 3.71)	(1.13 ; 1.53)
σ_{ϕ_1}				0.03
				(0.019 ; 0.04)
σ_{ϕ_2}	0.012	0.23		
	(0.004 ; 0.020)	(0.16 ; 0.31)		
σ_{ϕ_3}			0.001	0.21
			(0.001 ; 0.100)	(0.10 ; 0.33
$\rho_{\phi_1\phi_3}$				0.74
				(0.32 ; 1.00)
Controlled Release				
θ_0	4.37	2.41	0.01	1.43
	(4.19 ; 4.56)	(2.19 ; 2.63)	(-0.22 ; 0.25)	(1.23 ; 1.63)
θ_1	-0.78	-0.17	-0.08	0.09
	(-0.93 ; -0.63)	(-0.33 ; -0.01)	(-0.10 ; -0.06)	(0.06 ; 0.12)

Table 1: Parameter estimates (95% confidence interval)
for Models 1–4. (continued)

	Model 1	Model 2	Model 3	Model 4
	Est.	Est.	Est.	Est.
Parameter	(95% CI)	(95% CI)	(95% CI)	(95% CI)
σ_2	0.56	0.53	0.68	0.66
	(0.54 ; 0.59)	(0.50 ; 0.55)	(0.64 ; 0.71)	(0.63 ; 0.70)

Table 2: Model Fit Based on the Criterion of Average Absolute Percent Prediction Error and its 90% confidence interval for Models 1–4.

Model	C_{max}		AUC_{last}		AUC_{0-4}	
1	82.95	(81.70 ; 84.22)	75.27	(73.19 ; 77.40)	76.92	(75.68 ; 78.18)
2	82.94	(81.83 ; 84.06)	74.06	(73.01 ; 75.13)	77.09	(75.82 ; 78.39)
3	8.06	(5.24 ; 12.40)	7.32	(5.13 ; 10.45)	8.46	(5.93 ; 12.08)
4	9.21	(5.54 ; 15.31)	4.67	(3.20 ; 6.83)	7.08	(4.34 ; 11.56)

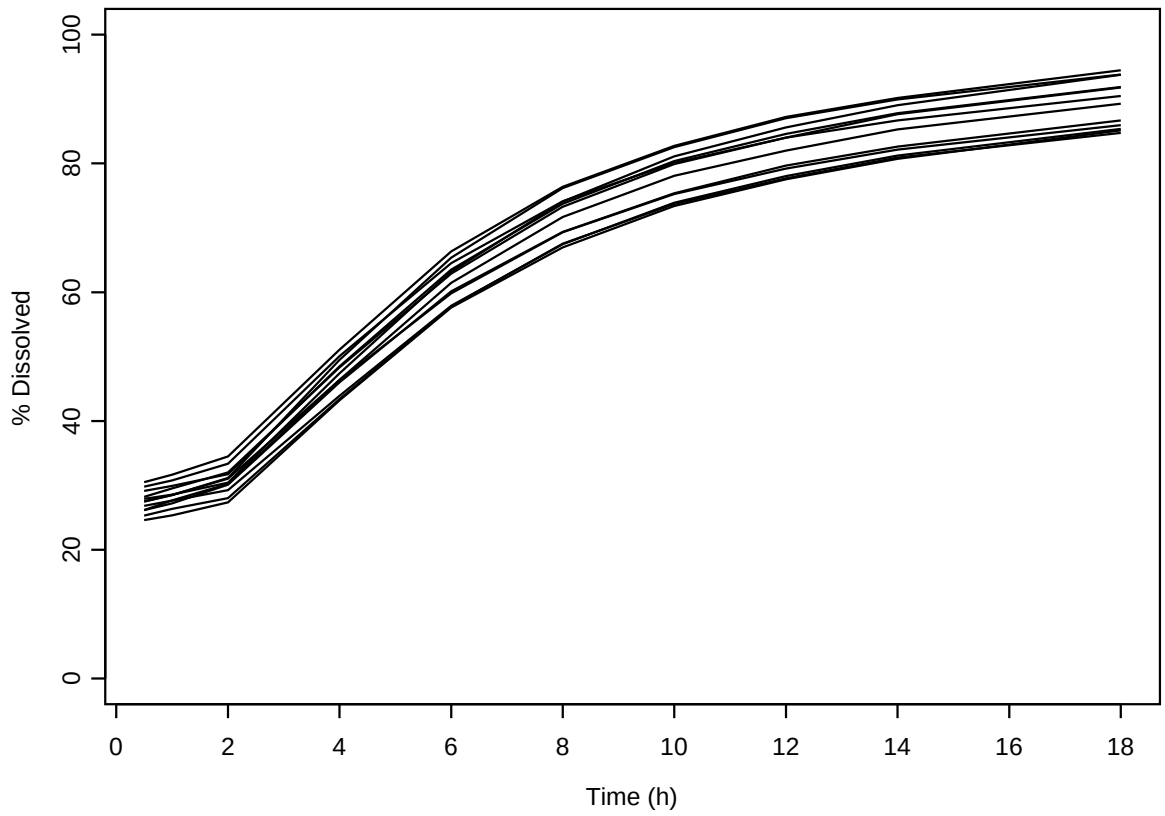

Figure 1: *In-Vitro* Dissolution Curves of Twelve Individual Capsules of the Controlled Release Formulation

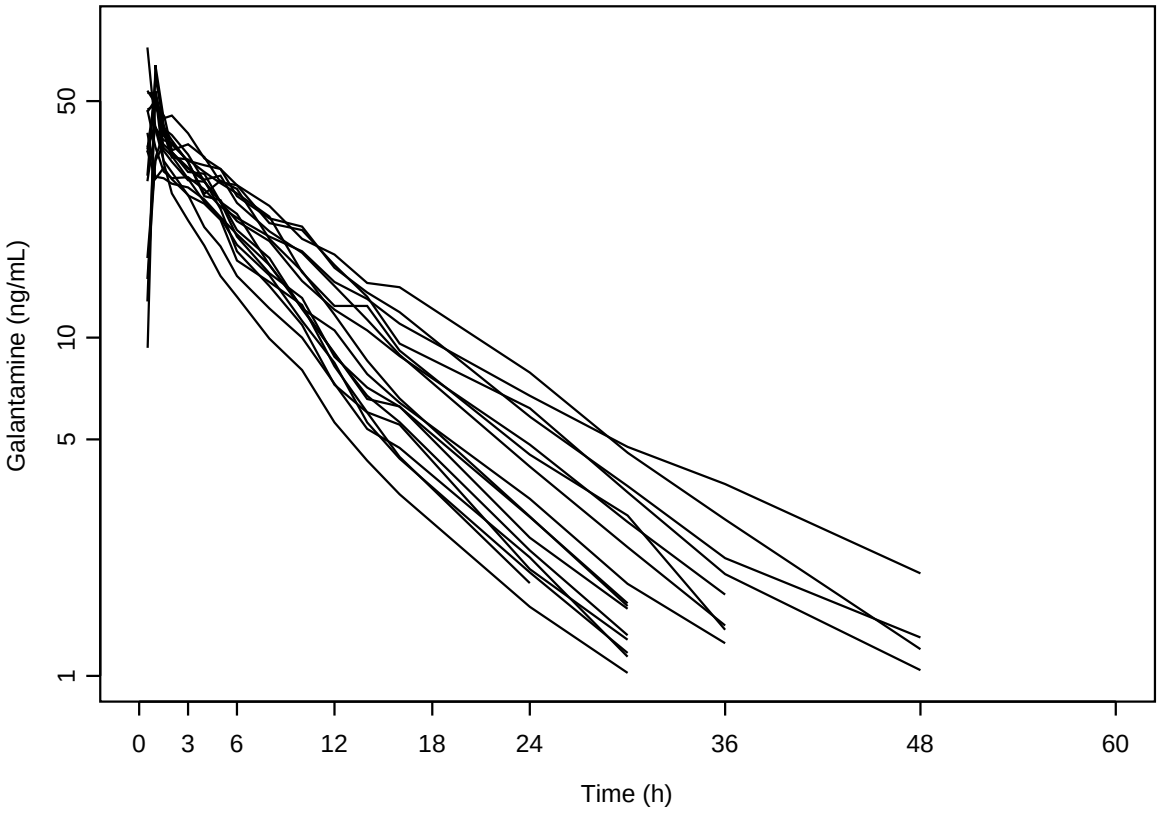

Figure 2: Individual *In-Vivo* Plasma Concentrations of 16 Patients for the Immediate Release Formulation of Galantamine.

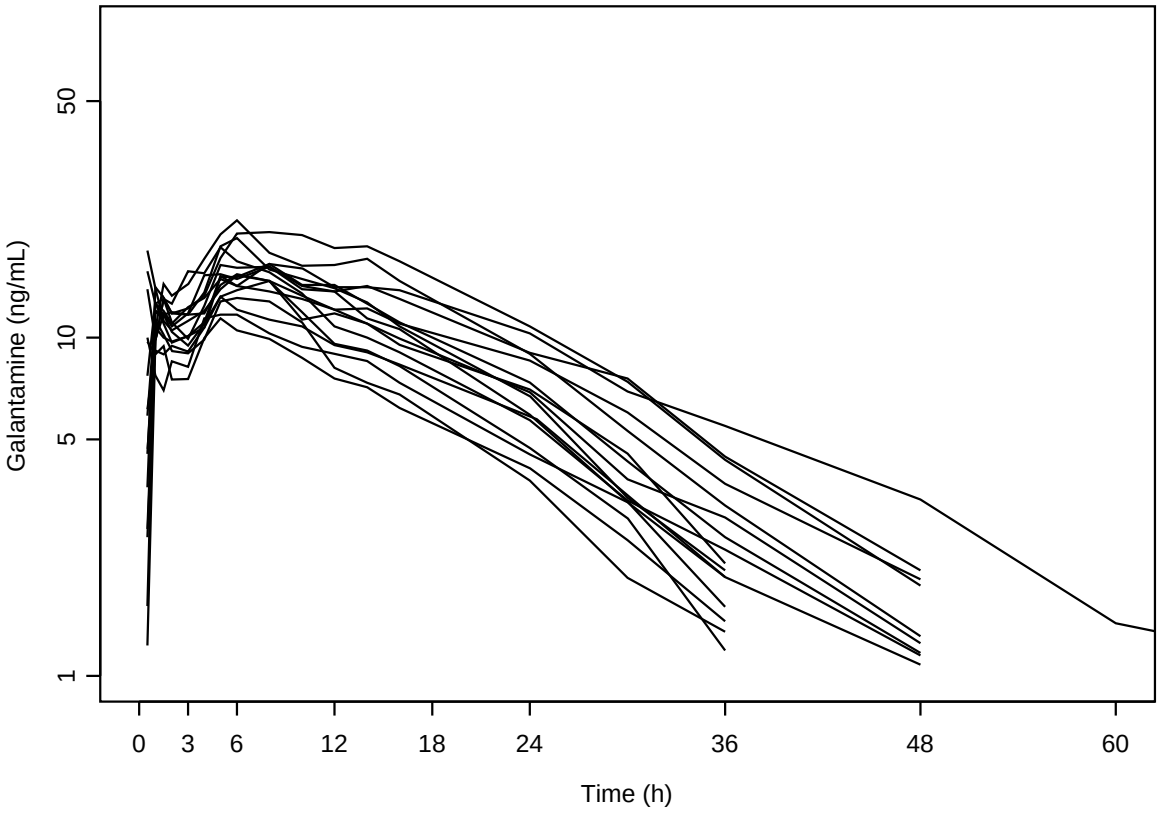

Figure 3: Individual *In-Vivo* Plasma Concentrations of 16 Patients for the Controlled Release Formulation of Galantamine.

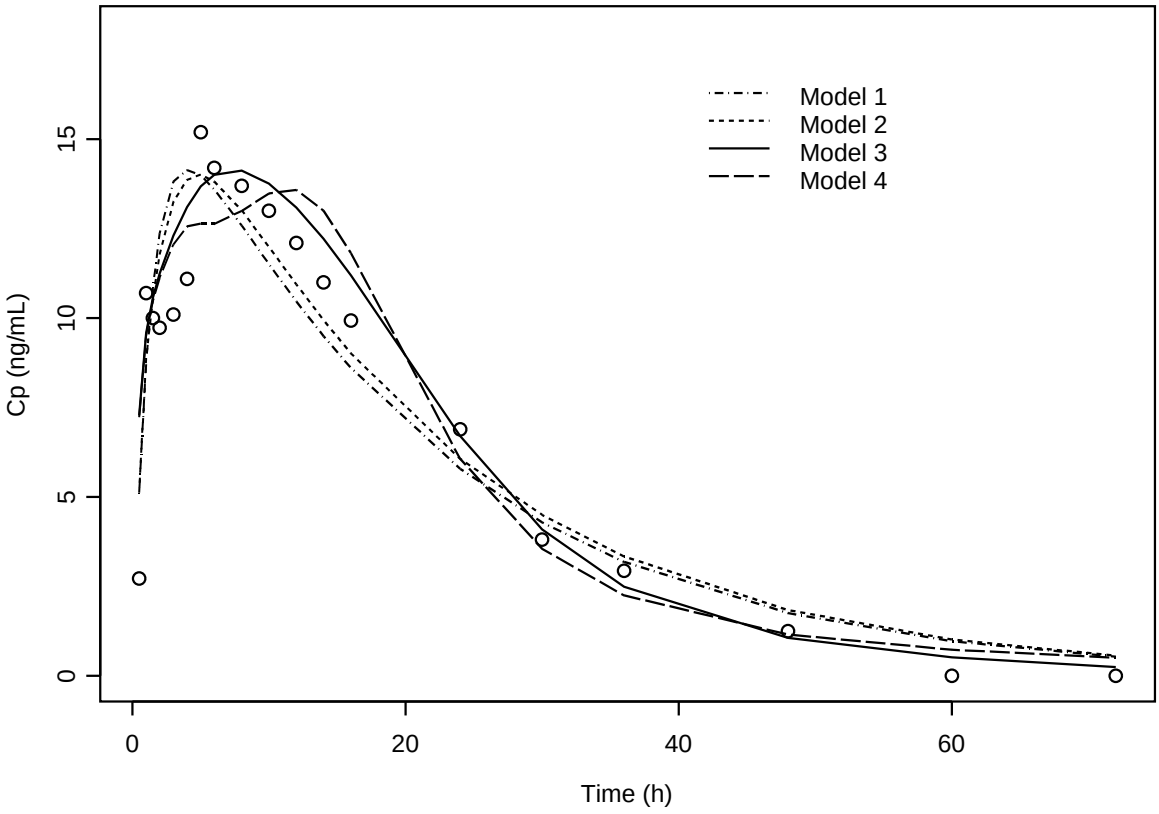

Figure 4: Observed and Predicted Controlled Release Galantamine Concentrations of one Randomly Chosen Subject for the Different Models.

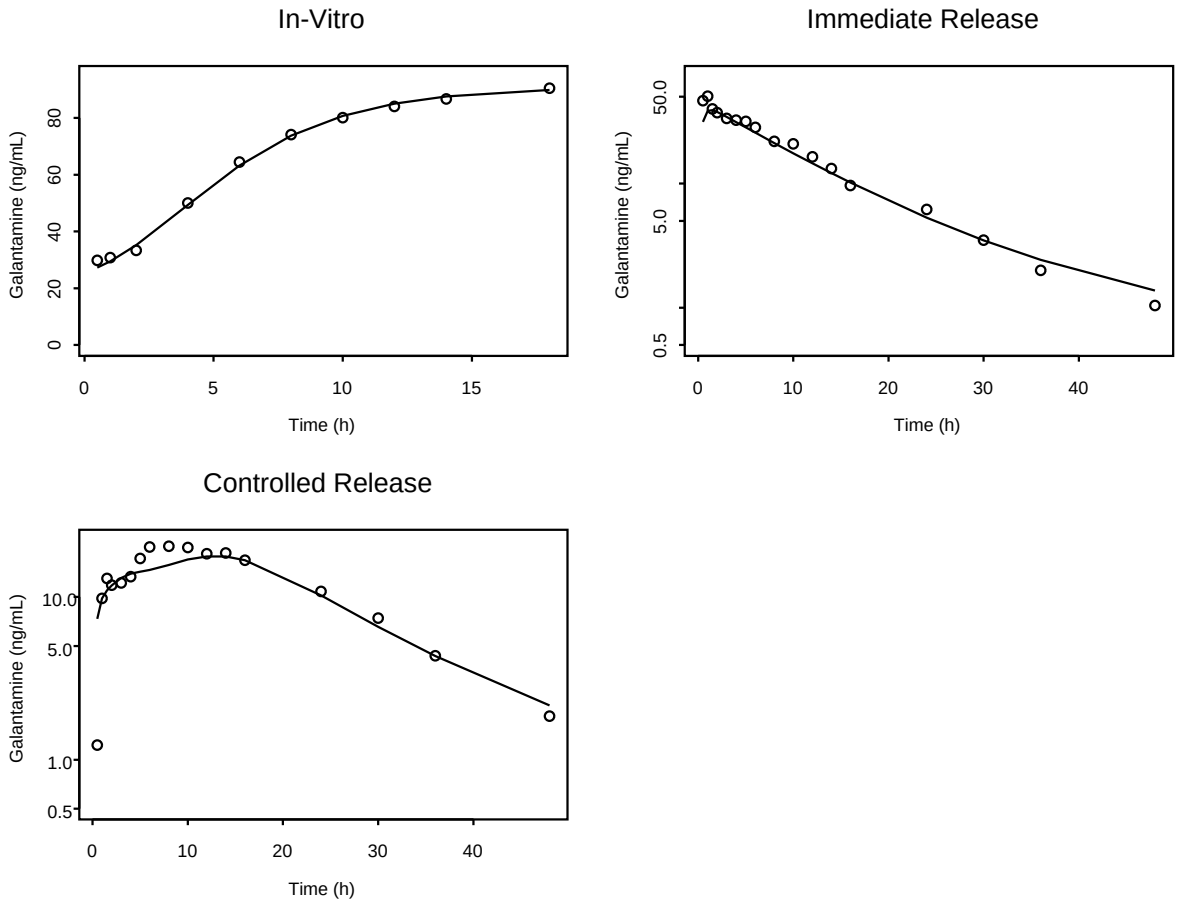

Figure 5: Observed and Predicted *In-Vitro* as well as *In-Vivo* Controlled and Immediate Release Galantamine Concentrations Time Profile for a Randomly Chosen Subject and Capsule. Predictions are Based on the Gompertz Odds Model.