A mixture distribution approach to IVIVC modeling of a dual component drug delivery system

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Background & Objectives

✓*In vitro* dissolution tests are routinely performed both to provide the necessary manufacturing process control and to determine the stability of the release rate characteristics of the product.

✓However, *in vitro* dissolution studies can be used for applications other than quality control of a product if they can be linked to its *in vivo* performance. This *in vitro-in vivo* relationship is known as *in vitro-in vivo* correlation (IVIVC).

✓The development of an IVIVC model can be beneficial in setting dissolution specifications or serving as surrogate for bioequivalence studies.

✓The objectives of this exercise were the further development of the non-linear mixed effects modeling approach described by OHara *et al.*[1] to allow simultaneous analysis of more than one formulation and to establish an IVIVC for a dual-component drug delivery system. Data collected on the drug galantamine, which is used in the treatment of Alzheimer's disease[2,3,4], was used to illustrate the applicability of this modeling technique.

Model Description

✓The nonlinear mixed effects IVIVC modeling approach, originally described by OHara *et al*[1]., was extended as follows:

Firstly, to enable the model to fit more than one formulation at a time, the shape of the dissolution curve was described by a function A(ϕ,t) instead of estimating a parameter for every observation time point. As a result, fewer parameters were needed to describe the fraction dissolved for every formulation.

Secondly, to describe the dual-component drug delivery system:
- the *in vitro* data were described as a mixture of two distributions i.e. the fraction of the typical tablet from formulation *h* dissolved *in vitro* at time t was given by:

$$F_h(t) = f_h + (1 - f_h) * A(\phi, t)$$

with f_h represents the fraction of the total dose that instantly dissolves.

- the *in vivo* plasma concentration for the k^{th} subject was described using a mixture of immediate release (IR) and controlled release (CR) components using:

$$Cp_k(t) = f_h D C_{dk}(t) + (1 - f_h) D \int_0^t C_{dk}(t-\tau) F'_k(\tau) d\tau$$

where *D* is the dose administered and $C_{dk}(t)$ and $F_k'(t)$ are the unit impulse response and the *in vivo* dissolution rate for that subject, respectively.

Methods

✓ Four controlled release (CR) formulations of galantamine were manufactured to have a delivery of 25% of the dosage as an IR dose and the remaining 75% as a CR dose.

✓16 healthy subjects were enrolled and received a single 8 mg dose of an immediate release (IR) of galantamine followed by a 4-way cross-over treatment period, where subjects received single 8 mg doses of four CR formulations (Slow, Medium, Fast and External) of galantamine, in a random sequence.

✓Three of the four CR formulations (Slow, Medium and Fast) were used for the development of the IVIVC model, which was used to predict plasma concentration-time profiles for each subject following administration of all four formulations.

✓The model described above was fit to the *in vitro* and *in vivo* data simultaneously using a custom-written PRED subroutine for NONMEM® V[5]. All model fitting was carried out at the individual subject/dosage unit level.

✓Internal predictability was assessed using the three formulations included in the model development, while the fourth was used to evaluate external predictability. The AUC and C_{max} were calculated for the observed and predicted profiles and used to compute the percentage prediction errors in accordance with the FDA validation guideline[6].

Results

✓ Consistent with the *in vitro* dissolution rank order, the slow release formulation had the lowest mean C_{max} and the highest mean t_{max}; while the fast release formulation had the highest mean C_{max} and the shortest mean t_{max} (16.2 *vs.* 22.4 ng/mL and 5.91 *vs.* 4.81 h, respectively) (Figure 1).

✓The average of predicted and observed *in vitro* and *in vivo* data per formulation are shown in Figure 2 and 3, respectively, and demonstrate a good model fit.

✓ The calculated prediction errors for both the internal and external predictability comfortably met the FDA criteria (Table 1). This means an average absolute prediction error of less than 10% for C_{max} and AUC for internal predictability. In addition, the prediction error for each formulation should not exceed 15%. For external predictability, the %PE for C_{max} and AUC must be less than 10%.

Table 1: Internal and External Predictability of the IVIVC Model

Internal Predictability

Treatment	$C_{max,obs}$ (ng/mL)	$C_{max,pred}$ (ng/mL)	[%PE] C_{max}	AUC_{obs} (ng.h/mL)	AUC_{pred} (ng.h/mL)	[%PE] AUC
Medium	17.0	16.4	3.51	379	362	4.51
Slow	15.3	14.5	5.61	383	372	2.79
Fast	21.6	20.3	6.33	399	367	8.06
Mean [%PE]			5.15			5.12
External Predictability						
External	15.2	14.8	3.00	390	364	6.86

Figure 1: Mean *In Vitro* Dissolution and Mean Plasma Concentration-Time Profiles of the four CR formulations

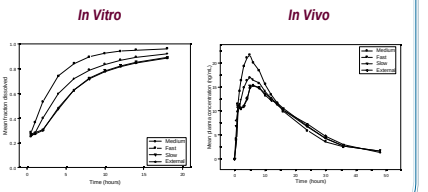


Figure 2: Mean Predicted and Observed Fractions Dissolved

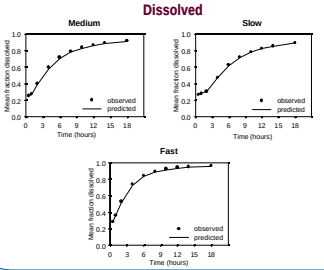
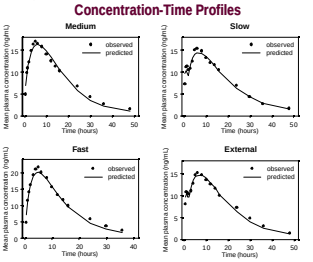


Figure 3: *In Vivo* Mean Predicted and Observed Concentration-Time Profiles



Conclusion

✓The non-linear mixed effects modeling approach described by O'Hara *et al.*[1] was extended to analyze more than one formulation simultaneously;

✓A mixture distribution-based model was developed to describe a dual-component drug delivery system. This model was incorporated into the nonlinear mixed effects model[1];

✓The updated model was successfully applied to the galantamine formulations that have IR and CR components

✓The fitted IVIVC model met the FDA criteria for internal and external predictability.

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