Establishment of preclinical mechanistic in vitro-in vivo correlations for long-acting injectable suspensions

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PURPOSE

Long acting injectable (LAI) formulations administered through subcutaneous (SC) or intramuscular (IM) routes provide sustained drug release over an extended period. For LAIs formulated as crystalline suspensions, the extended release is obtained through the formation of an *in-situ* drug depot at the injection site from which poorly soluble drugs slowly dissolve and are subsequently absorbed into the systemic circulation[1].

The development of complex generic LAIs is challenging since the relationship between solubility, particle size, and *in vivo* release from a parenteral suspension has not yet been established systematically. In this scenario, the use of modeling and simulation may provide a unique opportunity to mechanistically understand the *in vivo* release of drug from LAI suspensions and drug disposition. Establishing mechanistic *in vitro-in vivo* correlations (IVIVCs) is a valuable approach to further drug product development of LAIs.

OBJECTIVE

The objective of this study was to use different modeling approaches to mechanistically understand the *in vivo* performance of LAIs in preclinical species and to establish an IVIVC. Depo-SubQ Provera 104®, a SC suspension of medroxyprogesterone acetate (MPA), was used as a model drug product.

METHODS

A mechanistic PBPK model for MPA was built using GastroPlus® 9.8.2. All tissues were modeled as perfusion-limited tissues, the tissue/plasma partition coefficients were calculated using the Lukacova method, and the physicochemical and biopharmaceutical properties were obtained from the literature[2] or predicted from the structure of MPA using ADMET Predictor® 10.3. According to the literature[3], there can be a 1 to 3-fold increase in depot volume over time due to tissue inflammation, hence this process was included in the PBPK model. The same fold increase in depot volume was used across all formulations, i.e., reference listed drug (RLD) of MPA and formulation variants (by varying excipient quantity or manufacturing process). The in vitro and in vivo studies in rabbits were obtained from literature[4] and from a collaboration with Dr. Burgess's laboratory at the University of Connecticut.

Approaches taken to predict the in vivo dissolution:

1. Drug's solubility and particle size distribution
   - Due to particle aggregation, the *in vitro* particle size distribution was scaled to an *in vivo* effective particle size to capture the observed PK profile. The same scaling was used across all formulations [the mean radius and standard deviation (SD) fitted to the D10, D50, D90 data were increased 1.8- and 4.8-fold, respectively].
2. Mechanistic IVIVC - Time scaling through Levy plots
   - IVIVC was established with formulations F1, F2 and F3 (internal validation) and the reference product, Depo-SubQ Provera 104®, was used as an external validation

RESULTS

- The developed PBPK model for MPA adequately described the plasma pharmacokinetic (PK) profile of MPA following intravenous (IV) administration in rabbit (R^2>0.77).
- The experimental particle size distribution resulted in overprediction of Cmax and AUC (data not shown), whereas the scaled particle size distribution resulted in more adequate prediction (Figure 1).
- The inclusion of inflammation parameters in the model resulted in better Cmax prediction with a lower average absolute prediction error (PE) (11% ±5.2) while maintaining AUC average absolute PE <10% and PE <15% for each formulation.
- As shown in Figure 2, the IVIVC using the time scaling approach resulted in an overall reasonable prediction of plasma concentrations for rabbit. The Cmax and AUC %PEs were within 12.3% and 17.8%, respectively. The average absolute PE for Cmax was 9.1% (±8.6) and 9.2% (±10.7) for AUC. The %PEs for each formulation are given in Table 1.

Table 1. *Comparison of Cmax and AUC prediction errors after SC administration of the three test formulations and RLD.*

		F1			F2			F3			RLD		
		Obs.	Sim.	%PE	Obs.	Sim.	%PE	Obs.	Sim.	%PE	Obs.	Sim.	%PE
Scaled PSD	Cmax (ng/mL)	9.96	7.53	**-24.38**	8.82	5.84	**-33.71**	7.46	7.61	**2.06**	8.9	6.69	**-24.82**
	AUC 0-t (ng-h/mL)	8435.7	9478.3	**12.36**	7659.9	7556.8	**-1.35**	8714.3	9527.9	**9.34**	9229.6	9053.7	**-1.91**
Scaled PSD & Inflammation	Cmax (ng/mL)	9.96	10.98	**10.20**	8.82	7.72	**-12.44**	7.46	8.72	**16.9**	8.9	9.28	**4.25**
	AUC 0-t (ng-h/mL)	8435.7	9193.4	**8.98**	7659.9	7273	**-5.05**	8714.3	9802.7	**12.5**	9229.6	8730.6	**-5.41**
		F1			F2			F3			RLD		
		Obs.	Sim.	%PE	Obs.	Sim.	%PE	Obs.	Sim.	%PE	Obs.	Sim.	%PE
IVIVC F1/F2/F3	Cmax (ng/mL)	9.96	8.85	**-11.18**	8.82	9.56	**8.46**	7.46	7.80	**4.57**	8.9	9.99	**12.3**
	AUC 0-t (ng-h/mL)	8435.7	8183.9	**-2.98**	7659.9	6970.7	**-9.00**	8714.3	9333.4	**7.10**	9229.6	10870	**17.77**

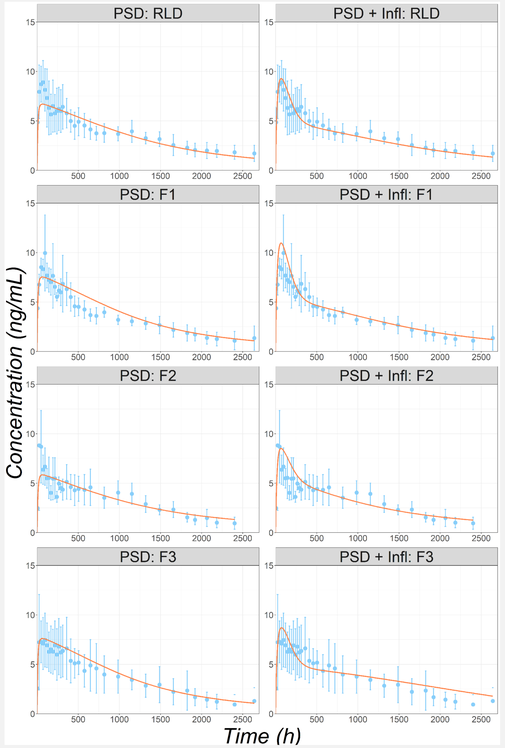

Figure 1. *Observed (blue circles) and predicted (orange line) PK profiles after SC administration of different MPA LAI formulations in rabbits. Prediction based on in vivo particle size distribution (PSD) using the same scaling across all formulations. PSD: No inflammation considered, and PSD + Infl: Inflammation parameters included. RLD: Reference Listed Drug*

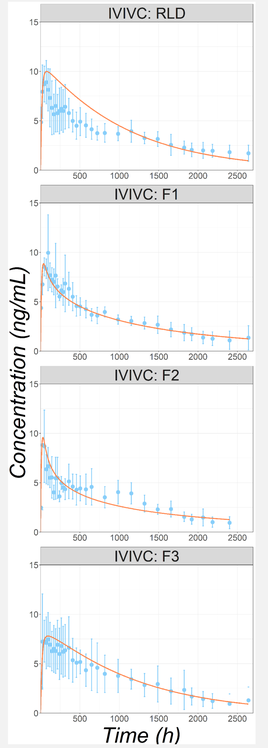

Figure 2. *Observed (blue circles) and predicted (orange line) PK profiles after SC administration of different MPA LAI formulations in rabbits. Prediction based on mechanistic IVIVC.*

CONCLUSIONS

- Utilizing the same scaling between *in vitro* and *in vivo* particle size distribution across all the formulations and varying depot volume over time (due to inflammation) resulted in reasonable prediction of MPA PK profiles.
- The larger effective *in vivo* particle size can be related to *in vivo* particle aggregation. This shows the utility of *in silico* tools for mechanistic understanding of *in vivo* product performance.
- The mechanistic IVIVC approach also resulted in reasonable predictions of MPA profiles as demonstrated by average absolute %PE <10% for both Cmax and AUC.
- Establishing IVIVC for LAIs is challenging given the need for time scaling (seen by the higher AUC %PE for RLD), hence further studies are needed to refine this approach.

FUNDING, DISCLAIMER AND REFERENCES

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